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PLACENTOGRAPHY IN ANTE-PARTUM HAEMORRHAGE

BY

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FOR some years, soft tissue radiography has been increasingly adopted in Great Britain in the localization of the placental site, and many obstetric units employ this technique as a diagnostic measure in cases in which placenta praevia is suspected. No doubt exists today regarding the accuracy of the method, as has been shown by a number of writers including Reid (1949), Whitehead (1953), Hartley (1954), Percival and Murray (1955), Lindsay and Davidson (1956) and Crawford *et al.* (1957).

Quite recently, however, Macafee (1960a) said that he believes that there is little place for placentography in the management of ante-partum bleeding and that he has not employed it in his hospital for some years. This view has received support from Charles (1959), Stallworthy (1959), Vartan (1959), Williams (1959), Browne (1960) and Theobald (1960).

On the other hand, certain obstetricians, including Percival and Murray (1955, 1960a) and Watson *et al.* (1957), are strongly of the opinion that placentography can play an important part in the management of ante-partum haemorrhage. These writers have found that patients who have had a slight "non-toxic" accidental haemorrhage may be allowed home with safety once the presence of placenta praevia has been excluded by soft-tissue radiography. The advantages of this to the patients are obvious and valuable antenatal beds are released for other purposes. Macafee (1960b, c) disagrees with this view and says that these patients should be kept in hospital. He says that the foetal mortality in these cases is considerable and quotes Barnes as having a foetal mortality of 27·8 per cent in her cases of "non-toxic" accidental haemorrhage. In his own cases of accidental haemorrhage, 245 out of 360 were of "non-toxic" type and the foetal mortality was 27·3 per cent.

In a previous paper (Crawford *et al.*, 1957), the writers analyzed the results obtained by the use of placentography in the management of ante-partum haemorrhage. In this preliminary report, the conclusions reached were essentially similar to those of Percival and Murray (1955) and Watson *et al.* (1957). Since then, the method has been employed in a much larger series of cases and the purpose of the present communication is to review these results.

TECHNIQUE OF PLACENTOGRAPHY

In developing the radiological technique for soft tissue placentography, the aim has been to combine accuracy with the minimum of radiation to the mother and foetus. The recent reports by the Medical Research Council (1956) and by Stewart *et al.* (1956, 1958) have emphasized the necessity for such a method. The Adrian Committee (Ministry of Health, 1959), however, declared that there should be no hesitation in undertaking such investigations as placentography and pelvimetry when these are indicated. Hartley (1960) questions the risk to the foetus in placentography and says that, if there is a risk, it must be an exceedingly small one. Percival and Murray (1960b) take a similar view and say that the risks to the foetus of

placentography have been greatly exaggerated. They find that one film is usually sufficient and that four are hardly ever required. The desirability of employing a single film has also been stressed by Earn *et al.* (1958). With the technique to be described, in the great majority of cases, one film is sufficient. Many workers use more than one film, however, some employing two and others three.

The technique employed in the earlier cases in the present series has been described in a previous communication (Crawford *et al.*, 1957). In the last 2 years, the method has been modified as follows:

To achieve satisfactory results with one film, a filter is essential. Of all the filters tried, the water-pillow has given the most constant results. This filter is flexible, moulds itself to each patient and at the same time sustains the abdomen in the lateral position.

One size of water-pillow is used for all patients. This pillow measures 22 inches by 18 inches and contains 6 pints of water, to which is added 260 ml. of "Pyelosil" or similar preparation. This size of water-pillow accommodates all sizes of patients. When a small patient is being examined, a sand-bag is placed over the portion of the pillow which projects posteriorly, to force the water forwards. For the filter to be effective, most of the water must lie under the anterior part of the abdomen. Ilford "Fluorazure" screens are used. An average case, at about 36 weeks of pregnancy, requires a kilovoltage of about 77 and with 200 milliamperes the exposure is about 0·8 second. The anode-film distance is 42 inches, with a 6-inch cone. The Bucky ratio is 10 to 1. This is a method which, if not carried out by a radiologist, should be done under his supervision. At the Southern General Hospital, Glasgow, all cases of suspected placenta praevia are X-rayed by the radiologists, with the full approval of the radiographers.

Placentography is seldom attempted before the 32nd week of pregnancy. By that time the foetal fat line is usually present and this line demarcates the foetus from the surrounding tissues. In view of this, cases are not referred for X-ray examination until there is every possibility of the placenta being demonstrable. It seems to be a common belief that successful placentography depends on the foetus presenting by the vertex. This is not so. With this method, the placenta can be shown, irrespective of the foetal presentation.

Using this technique, almost all placentae can be seen in the lateral projection; the exceptions are those implanted laterally which occurs in about 1 per cent of cases.

Lateral implantation should be demonstrable in the antero-posterior view but, since only 5 such cases have occurred in this series, it is not possible to be definite on this point.

It is generally assumed that the shadow density of the placenta, amniotic fluid and uterine wall are identical, and while this is so when the placenta is small, a well-developed placenta has a greater density than the other soft tissues. Calcification of the placenta is not a common finding and it has been extensive on 3 occasions only. With this technique, the placenta is usually so obvious that the demonstration of calcification plays no part in its localization.

Present Series

During the period from 1st January, 1949 to 31st December, 1958, 1,234 cases of ante-partum haemorrhage were admitted to the Obstetrical Department of the Southern General Hospital, Glasgow. In a further 34 cases with no history of ante-partum bleeding, placenta praevia was discovered and these cases have been included in the present series. These 1,268 cases can conveniently be divided into 2 groups. The first of these consists of cases treated before the introduction of soft tissue placentography in December, 1952 and, the second, of cases treated after the routine adoption of this technique.

Group 1. Cases Treated Before the Introduction of Placentography

In this group there were 340 cases of ante-partum haemorrhage and 10 cases of placenta praevia without ante-partum bleeding. Two hundred and three of these 340 patients with ante-partum haemorrhage required immediate operative treatment or were delivered soon after admission. The details are shown in Table I.

TABLE I

Cases of Ante-partum Haemorrhage Requiring Immediate Treatment or Delivery Within 48 Hours of Admission

Clinical Findings	Total Cases	Number with Placenta Praevia
Concealed or mixed accidental haemorrhage	57	0
Excessive bleeding	24	7
In labour on admission or within 48 hours	57	8
At or near term	65	29
Total	203	44

The remaining 137 cases of ante-partum haemorrhage in this group were treated expectantly, according to the method advocated by Macafee (1945), for periods varying from 7 to 73 days. In each case the foetus was viable when the patient was admitted but the duration of pregnancy was less than 37 weeks.

Expectant treatment was terminated in a few instances by the onset of premature labour or by elective Caesarean section for other obstetric indications. In the remaining cases, vaginal examination was carried out under general anaesthesia, usually at the end of the 37th week of pregnancy, when the foetus was judged to be reasonably mature. This examination was carried out in the operating theatre, with preparations completed for delivery by Caesarean section if necessary. In this group of 137 patients treated expectantly, 29 cases of placenta praevia were found.

In the remaining 10 patients, in whom ante-partum haemorrhage did not occur, placenta praevia was diagnosed either at Caesarean section for other obstetric indications, or during operative vaginal delivery, when the low placental implantation was detected by direct palpation. Thus, in the first group of 350 patients, there were 83 cases of placenta praevia. In Table II the mode of delivery and the maternal and foetal results are shown for all cases in this group.

It is apparent from this Table that Caesarean section was the treatment of choice in the great majority of cases, but artificial rupture of the membranes was preferred in the management of some Type I cases, particularly those implanted on the anterior uterine wall. In general, podalic version, bringing down a leg in breech presentation and the application of Willett's forceps, were reserved for the few cases in which the foetus was dead, immature or congenitally deformed. The Caesarean section rate was 76 per cent and the lower uterine segment operation was employed in all but 4 cases.

No maternal death occurred in these 83 cases of placenta praevia. The perinatal mortality rate in 88 babies, including one case of triplets and 3 cases of twins, was 25 per cent. One of the stillborn babies delivered vaginally was anencephalic. Of the remaining 21 stillbirths and neonatal deaths in this group, 17 were of premature babies and 8 of these weighed less than 4 pounds at birth.

For purposes of comparison with the second group of cases, the average number of days spent in hospital antenatally by the cases treated expectantly in the first group has been estimated. It was decided to compare the interval between the date of admission and the date of vaginal examination or delivery in each

TABLE II

Results of Treatment of Cases of Placenta Praevia in Group 1

Mode of Delivery	Total Cases	Maternal Deaths	Total Births	Total Stillbirths and Neonatal Deaths	Perinatal Mortality Rate %
Caesarean section ..	63	0	65	10	15·4
Vaginal delivery ..	20	0	23	12	52·2
Total	83	0	88	22	25

TABLE III

Cases of Ante-partum Haemorrhage in Group 2 in Which Soft Tissue Radiography was Not Carried Out

Clinical Findings	Total Cases	Number with Placenta Praevia
Concealed or mixed accidental haemorrhage	111	0
Excessive bleeding	55	36
In labour on admission or before soft tissue radiography could be carried out	98	14
At or near term	14	7
Severe pre-eclampsia	1	0
Total	279	57

group. In this group of patients treated before the introduction of soft tissue radiography, in which expectant treatment was carried out, the average time spent in hospital antenatally was 18·9 days.

Group 2. Cases Treated After the Introduction of Placentography

Of this group of 918 cases, 894 were admitted with ante-partum haemorrhage and there were 24 additional cases of placenta praevia without bleeding. Two hundred and seventy-nine patients admitted with ante-partum haemorrhage required immediate operative treatment or were delivered shortly after admission, and these cases were not considered suitable for investigation by soft tissue radiography. The details are shown in Table III.

Although proximity to term alone is not a contra-indication to the investigation of ante-partum haemorrhage by placentography, in the 14 cases in this category shown in Table III, it was considered desirable, for additional obstetrical reasons, to proceed immediately with the clinical investigation and not to wait for X-ray examination.

Two cases in this group are of particular interest and represent examples of the rare combination of placenta praevia and placenta accreta. In each case, removal of the placenta at Caesarean section was very difficult and hysterectomy had to be carried out because of persistent bleeding. In this connexion, Barry and Feeney (1958) found 7 cases of placenta praevia accreta in their large series of 609 cases of placenta praevia. In a further case of placenta praevia, uncontrollable bleeding was encountered at Caesarean section after removing the placenta and it was finally found necessary to carry out hysterectomy.

In the remaining 615 cases of ante-partum haemorrhage, soft tissue radiography was carried out, and this technique was also employed in a small number of additional patients in whom placenta praevia was suspected for various reasons, in spite of the absence of bleeding. In this latter group, there was either a history of recurrent malpresentation in the present pregnancy or the presenting part was unusually high. Percival (1959) states that by far the most common indication for placentography in his series of cases was a high head. He also stresses the fact that the term "high head" should be reserved for cases in which the head lies above the pelvic brim.

The radiological examination was carried out as soon as possible after admission, provided that the maturity of the pregnancy was not less than 32 weeks. There were 87 cases of placenta praevia in these 615 cases and, of these, 75 were correctly diagnosed by soft tissue radiography. In 2 further cases, the initial placentography was inconclusive and a repeat was requested, but further bleeding necessitated immediate delivery before this could be carried out. Seven of the remaining 24 cases without bleeding had ante-partum placentography and a correct radiological diagnosis was made in 5 of these.

Where there was radiological evidence of placenta praevia, the patients were kept in hospital until the end of the 37th week of pregnancy, or until the foetus was judged to be of

reasonable maturity, and then examination under anaesthesia was carried out in the operating theatre. In the more recent cases in the series, this vaginal examination was omitted if there was clinical and radiological evidence of a major degree of placenta praevia. The subsequent management depended on the findings and, where Caesarean section was employed, it was invariably of the lower uterine segment type. Thus the management of these cases was similar to those treated by the expectant method before the introduction of soft tissue radiography.

One case in which placentography showed what appeared to be anterior placenta praevia is of interest. On examination under anaesthesia, tissue indistinguishable from placental tissue was found to be lying over the internal os. Lower uterine segment Caesarean section was performed and the placenta was found to be in the upper uterine segment, the lower segment being occupied by a necrotic tumour which proved to be a leiomyosarcoma.

The patients in whom the placenta was shown radiologically to be in the upper uterine segment were examined vaginally as soon as possible after receiving the radiological report. During the first 12 months of this phase of the investigation, the examination was carried out under general anaesthesia in the operating theatre, but since then, with increasing confidence in the radiological diagnosis, these cases have been examined in the labour ward without anaesthesia. When the absence of placenta praevia was confirmed in this way, the patient was allowed home next morning, provided that no other obstetrical complications were present.

The amount of bleeding in these patients, who were sent home after placentography and subsequent vaginal examination had excluded placenta praevia, invariably was slight. Any patient with considerable initial bleeding was not sent home but was kept in hospital until after delivery. This group, however, constituted a small percentage of the total number. In addition, all patients with recurrent bleeding, however slight, were kept in hospital or, if the fresh bleeding occurred after dismissal, they were re-admitted immediately. Cases in this category also were most infrequent. So far, the results obtained do not indicate that there is any need to keep the vast majority of mild cases of "non-toxic" accidental haemorrhage, in hospital after exclusion of placenta praevia.

In the second group of cases there were 168 with placenta praevia. The mode of delivery and maternal and foetal results are shown in Table IV.

The factors influencing the decision as to mode of delivery in each case were essentially the same as those described in Group 1. One hundred and fifty-nine patients were delivered by lower uterine segment Caesarean section, including 3 treated by Caesarean hysterectomy. Six had artificial rupture of the membranes followed by spontaneous vaginal delivery, 1 a breech extraction, and 2 spontaneous vaginal delivery without induction of labour. In this group the Caesarean section rate was 94·6 per cent.

No maternal death occurred and the uncorrected perinatal mortality rate in 171 babies, including 3 sets of twins, was 14·9 per cent. One of the babies delivered by Caesarean section for Type IV placenta praevia had multiple congenital abnormalities, including hydrocephalus, and died 15 days after birth.

TABLE IV

Results of Treatment of Cases of Placenta Praevia in Group 2

Mode of Delivery	Total Cases	Maternal Deaths	Total Births	Total Stillbirths and Neonatal Deaths	Perinatal Mortality Rate %
Caesarean section ..	159	0	162	23	14·2
Vaginal delivery ..	9	0	9	2	22·2
Total	168	0	171	25	14·9

Another infant was found to have congenital oesophageal atresia after Caesarean section, and died following surgical treatment in another hospital.

In one further case with persistent bleeding necessitating immediate operation, on admission to hospital the foetal heart was not heard. Of the remaining 22 stillbirths and neonatal deaths in this group, 15 were of premature babies, 8 weighing less than 4 pounds at birth.

In comparison with the cases treated expectantly in the first group, in which the average time spent antenatally in hospital was 18·9 days, the corresponding figure for the group of 615 patients investigated by placentography was 8·9 days. This represents a saving of 6,150 "patient-bed-days" over a period of 73 months.

Comments

There were no maternal deaths in either of the groups of cases of placenta praevia and no deleterious effects attributable to placentography were observed in any of the patients in the second group. The saving of an average of about 10 days in hospital for each patient who would previously have been treated expectantly is an obvious advantage, both to the patient and to the hospital. So far no adverse effects have been observed following the dismissal of most cases of "non-toxic" accidental haemorrhage after exclusion of a diagnosis of placenta praevia.

The technique of soft tissue radiography described earlier resulted in a correct radiological diagnosis of the placental site in all but 12 patients with ante-partum haemorrhage who were subsequently found to have placenta praevia. The first 2 errors in diagnosis occurred during the first year of the present investigation and failure to diagnose placenta praevia radiologically was attributed to technical inexperience in the first case and immaturity of the pregnancy in the second; the X-ray examination in the latter case was carried out in the 31st week of pregnancy.

In 5 further patients the placenta was implanted mainly on the lateral wall of the lower uterine segment and, after careful re-scrutiny of the standard lateral films, it was considered that an accurate radiological diagnosis was not possible without antero-posterior or oblique radiographs.

The uncorrected perinatal mortality rate of 14·9 per cent compares favourably with the figure of 25 per cent obtained in the first group and with the results of many published series.

Summary

An analysis has been made of the cases of ante-partum haemorrhage treated in the Southern General Hospital, Glasgow, between 1st January, 1949 and 31st December, 1958. During this period, 1,234 cases of this condition were admitted to the Obstetrical Department of the hospital.

The first 340 patients were treated before the introduction of placentography. Where applicable, expectant treatment was adopted and the average length of time spent in hospital by the patients treated expectantly was 18·9 days before delivery or vaginal examination. There were 83 cases of placenta praevia in this group, with no maternal deaths and a perinatal mortality rate of 25 per cent.

Eight hundred and ninety-four patients with ante-partum haemorrhage were admitted after the introduction of placentography. In 615 of these, placentography was carried out, the average time spent in hospital by these patients before delivery or vaginal examination being 8·9 days. In this group there were 168 cases of placenta praevia, with no maternal deaths and a perinatal mortality rate of 14·9 per cent.

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CLINICAL ASPECTS OF ANOXIC STILLBIRTH

BY

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A FOETUS which dies *in utero* must undergo some functional change prior to its death. Although foetal death may be rapid, e.g., in accidental haemorrhage, it is probable that in most cases death is preceded by functional changes in the foetus over a period of time. At present the clinical detection of foetal distress is limited to the observation of an abnormal foetal heart rate and rhythm and the presence of meconium in the liquor amnii. The frequency of diagnosis of foetal distress in 115 stillbirths delivered at Queen Charlotte's Hospital between 1957 and 1959 is shown in Table I. It is clear that the diagnosis of foetal distress is unsatisfactory since it is rarely made even when severe foetal anoxia is present.

A detailed clinical study of the 69 patients with anoxic stillbirths has been made in an attempt to determine the possibility of improving foetal results by methods other than recognition of foetal distress.

Pre-eclamptic toxaemia, accidental haemorrhage and hypertension were the most common known causes of anoxic foetal death (Table II) Pregnancy had proceeded two weeks beyond the expected date of delivery in 11 cases but its role in causing stillbirth was difficult to assess as in 8 of these patients another possible cause of foetal death was present.

TABLE I

Diagnosis of Foetal Distress in 115 Stillbirths

	Number of Stillbirths	Diagnosis of Foetal Distress
All stillbirths	115	22 (19%)
Anoxic stillbirths ..	69	20 (29%)
Ante-partum ..	39	2
Intra-partum ..	30	18

PRE-ECLAMPTIC TOXAEMIA

In 3 primigravidae mild pre-eclamptic toxaemia was present on the expected date of delivery; the pregnancy was allowed to continue and foetal death occurred seven, eleven and twelve days respectively after term. In addition, 2 foetal deaths occurred between the 38th and 40th week in patients with mild pre-eclampsia.

A primigravida aged 25 years was admitted to the antenatal ward at 39 weeks with a blood pressure of 150/90 mm. Hg and a trace of protein in the urine; during the following seven days these signs persisted despite rest in bed; the pregnancy was allowed to continue. On the expected date of delivery the foetal heart was not heard and spontaneous delivery of a stillborn infant followed.

It would seem, therefore, that the risk to the foetus of induction of labour after the 38th week of gestation in patients with mild pre-eclamptic toxaemia may be less than the continuation of pregnancy.

Three patients in the present series had slight oedema of the ankles and fingers and a blood pressure raised on more than one occasion to between 130/80 and 140/90 mm. Hg.

TABLE II

Anoxic Stillbirths: Cause, Time of Death and Diagnosis of Foetal Distress

Probable Cause	Number of Anoxic Stillbirths	Ante-partum Death	Intra-partum Death	Diagnosis of Foetal Distress
None	19	9	10	6
Pre-eclamptic toxaemia	16	8	8	7
Accidental haemorrhage	16	14	2	3
Hypertension	13	6	7	4
Ante-partum haemorrhage (cause unknown) ..	3	2	1	0
Prolapse of cord	2	0	2	0
Total	69	39	30	20

A primigravida, aged 28 years, had a blood pressure less than 130/80 mm. Hg until the 40th week of gestation, when it rose to 140/85 mm. Hg and there was slight ankle and finger oedema. The blood pressure was 120/90 at 41 weeks and in the 42nd week of pregnancy foetal death occurred following the spontaneous onset of labour.

Although the definition of mild-pre-eclampsia is difficult it would be wise to consider patients with slight ankle and finger oedema and a rise of blood pressure above 130/80 mm. Hg as having pre-eclamptic toxaemia with an associated increased risk of foetal death.

Another difficulty in the management of mild pre-eclamptic toxaemia is that, although the signs of the disease may disappear when the patient is treated by rest in hospital or hypotensive drugs or diuretics, the hazard to the foetus may remain.

A primigravida, aged 23 years, three days before the expected date of delivery was admitted to hospital with a blood pressure of 130/90 mm. Hg, slight oedema of the fingers and ankles and a trace of protein in a catheter specimen of urine. Within 48 hours of admission to hospital the oedema and proteinuria had disappeared, although the blood pressure was still 130/90 mm. Hg. At seven days past term the foetal heart was not heard.

It would therefore appear advisable in the interests of the foetus to include patients with a blood pressure raised to between 130/80 and 140/90 mm. Hg and oedema of the fingers and ankles in the diagnosis of pre-eclamptic toxaemia; to remember that the disappearance of the signs of the disease does not necessarily mean it ceases to be a danger to foetal life; and, most important, to terminate pregnancy in any case of even mild pre-eclamptic toxaemia after the 38th week of gestation.

HYPERTENSION

Early

Hypertension occurred early, i.e., before the 20th week of pregnancy, in only 4 stillbirths, the blood pressure during pregnancy varying from 130/80 mm. Hg to 160/100 mm. Hg; foetal death occurred at 32, 38, 39 and 41 weeks of pregnancy. No case of severe hypertension resulting in foetal death was seen in the present series.

Late

In 9 patients the blood pressure was 140 mm. Hg systolic or 90 mm. Hg diastolic on at least two occasions during the latter half of pregnancy. In these cases the blood pressure had been less than 130/80 mm. Hg in early pregnancy and in 7 of the patients the rise in blood pressure occurred between the 38th and 42nd week of gestation. It is difficult to know whether these cases should be classified as mild pre-eclamptic toxaemia or late hypertension of pregnancy.

In 6 patients the rise in blood pressure was detected before the expected date of delivery and pregnancy was allowed to proceed beyond term.

A primigravida, aged 29 years, had blood pressure recordings during the last month of pregnancy of 150/80, 155/90, 145/90, 155/95 mm. Hg and the baby was considered small for the period of amenorrhoea. Five days after the expected date of delivery the blood pressure was 130/85 mm. Hg. A surgical induction of labour was performed two days after this and the foetus died during the first stage of a normal labour, and was apparently mature but only weighed 2,145 g.

In one patient, a primigravida aged 44 years, the blood pressure rose to 155/100 mm. Hg at the 39th week of gestation and at this time the foetus was thought to be small. The patient was admitted to hospital for rest and following this the blood pressure remained between 130/80 mm. and 140/90 mm. Hg; five days later the foetal heart was not heard.

In 4 of the 9 patients with late hypertension of pregnancy the foetus was thought to be small; this was confirmed following delivery and it is possible that the risk of foetal death is increased in late hypertension of pregnancy when the foetus is small.

The case records of 1,000 patients whose blood pressure was less than 130/80 mm. Hg during the first half of pregnancy were analyzed to determine the significance of a rise in blood pressure after the 20th week of gestation (Table III). The significance of the blood pressure recordings is limited because of the variable conditions under which it is taken in the antenatal clinics; more accurate readings could be obtained by standardizing the method of measurement of arterial pressure.

TABLE III

The Blood Pressure After the 20th Week of Gestation in 1,000 Patients Who were Normotensive (130/80 or Less) in the First Half of Pregnancy

Blood Pressure (After 20 Weeks)	No. of Cases
130/80 or less	542 (54%)
Over 130/80 to 140 systolic or 90 diastolic on one occasion	332 (33%)
140 systolic or 90 diastolic on at least two occasions, or higher	32 (3%)
140/90 or higher + oedema or proteinuria	94 (9%)

The stillbirth rate in the patients with a blood pressure rising to between 130/80 and 140/90 was the same as in the normotensive, 2 per cent, and therefore this rise in blood pressure by itself does not carry any increased hazard to the life of the foetus. Nevertheless, such a rise should always be carefully noted as it may be useful in making an early diagnosis of pre-eclamptic toxaemia. A rise of blood pressure on two occasions to at least 140 mm. Hg systolic or 90 mm. Hg diastolic occurred in only 3 per cent of deliveries and in a further study of these cases the stillbirth rate was found to be 6 per cent (11/192), 5 per cent being due to anoxia. This incidence is higher than the anoxic stillbirth rate of 1 per cent seen in all patients delivered in the hospital. As the majority of stillbirths in patients with this degree of hypertension occurred after the expected date of confinement, induction of labour should be performed in these cases by the 40th week of gestation.

IDIOPATHIC ANOXIC STILLBIRTHS

In 19 cases of anoxic stillbirth no definite cause of foetal death was present, although a number of abnormalities were detected during the antenatal period (Table IV).

Although there are theoretical reasons why any of these factors may cause foetal death their presence in the series could also be due to chance. Further study of each of these factors would be required to assess their role in the cause of foetal distress and foetal death.

TABLE IV

Antenatal Abnormalities in "Idiopathic" Anoxic Stillbirth

Antenatal Abnormality	No. of Cases
Repeated external version	3
Small foetus detected prior to foetal death	3
Haemoglobin under 70 per cent (10 g.)	4
Thyrotoxicosis	1
Threatened abortion	1
Multiple uterine fibromyomata	1
Patient scalded arm prior to cessation of foetal heart	1

Accidental Haemorrhage

Although the foetal heart was recorded frequently in the 16 cases of accidental haemorrhage foetal distress was diagnosed on only 3 occasions. In one case the foetal heart was irregular five minutes before it disappeared and in one the heart rate was 110/minute 30 minutes before the foetal heart sounds ceased; in the remaining case the foetal heart was 40/minute immediately prior to Caesarean section and the infant was stillborn.

More recently Caesarean section has been performed for foetal distress in patients with an accidental haemorrhage in an endeavour to diminish the perinatal mortality of this condition. The results of this treatment are shown in Table V.

One objection to the use of Caesarean section in accidental haemorrhage is that the operation may increase the risk of maternal death. In the severe case the use of blood transfusion and fibrinogen have made Caesarean section safer and when the foetus is alive the uterus will probably not yet be "couvelaire" and therefore may be expected to contract adequately after it is emptied. The survival of two out of three infants in the presence of a severe accidental haemorrhage with the foetal heart less than 100/minute would probably not have occurred if the management had been conservative.

Foetal Death in the Second Stage of Labour

In 15 of the 26 intra-partum stillbirths due to anoxia, foetal death occurred during the second stage of labour (in 4 patients the stage of labour at the time of foetal death was not recorded). The duration of the second stage was recorded as less than 30 minutes in 11 of the cases, 40 minutes in 3 and 100 minutes in 1. Hypertension or pre-eclamptic toxaemia was present in 11 of the 15 foetal deaths occurring in the second stage.

In view of the large proportion of these intra-partum anoxic deaths in the second stage, particularly in patients with maternal disease predisposing to foetal death, an attempt at their prevention should be considered, e.g., in patients with pre-eclamptic toxaemia or hypertension the foetal heart should be recorded more frequently in the latter part of the first stage of labour; auscultation immediately after the contraction may aid in detecting early foetal heart rate abnormality (McClintock, 1876). The use of forceps to shorten the second stage of labour in these cases should be considered; the risk to the foetus by the use of forceps is minimal if the obstetrician is experienced, local anaesthesia is used, and the presenting part has reached the mid-pelvis.

Summary

(1) The diagnosis of foetal distress is unsatisfactory as it was detected in only 29 per cent of anoxic stillbirths.

(2) A detailed clinical study of 69 cases of anoxic stillbirth was made to determine the possibility of improving foetal results by methods other than the detection of foetal distress.

Table V

Caesarean Section for Foetal Distress in Accidental Haemorrhage

Age	Parity	Shock	Tender Uterus	Tense Uterus	Blood Transfusion	Foetal Heart	Infant
29	0/1	+	+	+	2 pints	40–70	Alive
41	0/0	—	+	—	—	110	Alive
35	0/5	+	+	+	2 pints	90–40	Stillbirth
24	0/0	—	—	—	—	130–90	Alive
27	0/1	—	—	—	—	100–Irregular	Alive
27	0/0	+	+	+	2 pints	88–100	Alive
25	0/0	—	+	—	—	40	Stillbirth

(3) Termination of pregnancy is advised in all patients with even mild pre-eclamptic toxaemia after the 38th week of gestation.

(4) The anoxic stillbirth rate in 192 patients with late hypertension of pregnancy was 5 per cent; induction of labour should be performed in these cases by the 40th week of gestation.

(5) A large proportion of intra-partum anoxic stillbirths occur during the second stage of labour in patients with mild pre-eclampsia and late hypertension of pregnancy. In these cases forceps should be used to shorten the second stage.

ACKNOWLEDGMENTS

We are indebted to the consultant staff at Queen Charlotte's Hospital for access to case records of patients under their care.

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HYPERTENSION IN PREGNANCY AND ITS CONSEQUENCES

BY

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A QUARTER of a century has passed since the death of William Blair Bell, to whose memory this lecture is dedicated. In this time childbirth has become very much safer for both mother and child due to many factors, one of the most important being the very much improved standard of clinical care. We owe this in large measure to men of vision and foresight, under the inspiring leadership of Blair Bell, who founded this College.

Progress has been greatest in the technical aspects of obstetrics, particularly in the management of difficult labour. To a man of Blair Bell's originality, the relative lack of progress in our understanding of the pathology of pregnancy might have been disappointing. However there are signs that more interest is now being taken in preventing deviations from the normal physiological response to pregnancy which will doubtless lead to more rational methods of treating the pathological states. The subject of my lecture, pre-eclamptic toxaemia, can be used to illustrate this. Intensive clinical care can prevent the worst complications in most cases, especially for the mother, but the incidence of pre-eclampsia has not decreased and it is now the commonest cause of maternal mortality. In the most severe forms of the disease the foetal mortality is still high despite the best known treatment.

Treatment will remain empirical till the cause is discovered. In the meantime we must rely on early diagnosis, careful supervision, and interruption of the pregnancy when the progress of the disease cannot be arrested.

The problem of aetiology has been studied from many points of view. One of the most popular at present is the investigation of the basic biochemical changes occurring in the condition in the hope that they will explain the mechanism whereby hypertension, oedema and proteinuria are produced. These researches may include measurement of electrolytes, tissue spaces and hormones at various stages of normal and pathological pregnancy.

I have been interested in the problem of pre-eclampsia for some time and have studied variations in electrolyte and fluid balance in pregnancy but I feel sure that most workers in this field would agree with me that much more work must be done. I therefore do not propose to discuss this aspect of pre-eclampsia today. I will rather consider an entirely different approach to the problem, namely, its epidemiology. This method has not received much attention, possibly because of the difficulties inherent in any study of morbidity in a total population. A study of the epidemiology of pre-eclampsia has been made possible for me in Aberdeen since detailed and accurate records for all births in the City, irrespective of place of confinement, have been compiled for many years.

I hope to show that by this epidemiological approach it is possible to determine more precisely the types of women likely to develop pre-eclampsia. With this knowledge we may be able to detect the condition earlier and start treatment early enough to be more effective. Cases investigated in detail by the standard laboratory method should be chosen on sound epidemiological principles and aetiological theories based on them must agree with the epidemiological facts.

Interest in the prevention of eclampsia and in antenatal care in general began early in the present century. An important step forward was the recognition that hypertension preceded the albuminuria and eclamptic fits. It is not surprising that in the days when the finding of protein in the urine was regarded as the first sign of impending eclampsia, antenatal care failed to lessen the dangers appreciably. In recent years the study of weight changes in pregnancy has proved of some value in the early detection of pre-eclamptic toxaemia. Other measures used for this purpose, such as the flicker-fusion test and the cold-pressor test have proved to be of little value.

There is fairly general agreement that vascular changes are of major importance in pre-eclamptic toxaemia and it might be supposed that some indication of the early changes could be obtained by studying the pattern of the blood pressure which precedes pre-eclamptic toxaemia.

Unfortunately, this is far from simple for several reasons: (1) there is no unanimity regarding the definition of pre-eclamptic toxaemia; (2) there is disagreement on whether the amounts of rise in blood pressure or the level attained is of more importance; (3) blood pressure is notoriously difficult to record with accuracy; (4) large numbers would have to be studied; (5) to be of clinical value it should be possible to determine any susceptible group at a routine antenatal clinic using a commonly accepted method of measuring blood pressure; and (6) in order to rule out selection factors a total population should be studied.

It has been found possible for me to overcome at least some of these difficulties. Instead of studying pre-eclampsia defined as a rise of blood pressure to an arbitrary agreed level the changes in blood pressure at various stages of pregnancy have been related to certain pathological conditions occurring during the pregnancy. In this way a definition of pre-eclampsia is avoided.

Errors due to selection factors have been overcome since a very comprehensive records system, which includes blood pressure readings and weight change in pregnancy, is available for all pregnancies in the City of Aberdeen.

It was not possible to overcome the factor of observer error in the blood pressure recordings. This is virtually impossible to achieve because of the large number of cases involved.

This drawback has to be accepted since the nature of the investigation demands large numbers of cases. This technical deficiency indicates that the conclusions drawn from some of the findings must be accepted with caution. Nevertheless we believe that some most important conclusions can be drawn from this study.

In the first instance the records of 4,215 primigravidae with single births, who attended the antenatal clinics of the Aberdeen Maternity Hospital before the 20th week of pregnancy and were delivered there in the years 1950–55 inclusive, were selected for analysis. This group was chosen because accurate and detailed records were available from 1950 and previous to 1956 restriction of weight gain during pregnancy was not practised. Some 90 per cent of all primigravidae in the City of Aberdeen are booked for hospital confinement, so they may be considered as fairly representative of all primigravidae in the City. We have enough information about the other 10 per cent to know that this is in fact the case but they have been omitted since the facts about blood pressure readings and weight changes are not so detailed.

If we at this stage do not attempt to define pre-eclampsia but rather record blood pressure changes we must employ certain criteria of morbidity against which to test the variations in blood pressure and weight which occur.

These criteria were perinatal death, prematurity (baby weight under 5½ pounds) and the development of albuminuria (¼ g./L. or more), not due to urinary infection. Albuminuria, or more correctly proteinuria, has been included as it is generally recognized that in association with a rise of blood pressure in pregnancy it causes the prognosis to be much worse.

The distribution of the average diastolic and systolic blood pressures about 20 weeks are shown in Figure 1. The largest group have a blood pressure of 120/70–129/79 mm. Hg. Few have a blood pressure exceeding 140/90.

As age is known to influence blood pressure the distribution of the 20th week blood pressures

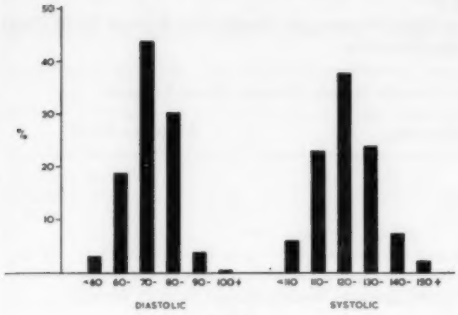

FIG. 1

Blood pressure levels at 20th week in 4,215 primigravidae.

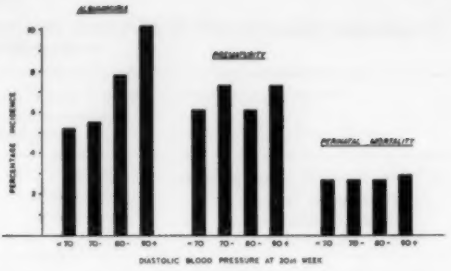

FIG. 2

Influence of diastolic pressure at 20th week on incidence of albuminuria, prematurity and perinatal mortality.

by age groups has been examined (Table I). The diastolic pressure remains unchanged until the age of 30 when it rises steadily. The systolic pressure on the other hand rises fairly steadily with age. This is similar to the findings of Miall and Oldham (1958) in non-pregnant women.

It seems therefore that the blood pressure at the 20th weeks of pregnancy is similar to that in the non-pregnant. We can therefore assume that, generally speaking, blood pressure readings taken after that time will measure pressure changes due to pregnancy. This is a fortunate finding since quite a proportion of primigravidae do not report for the first time until about the 20th week and they differ in some respects from those who attend earlier.

We wish now to study the relationship between the blood pressure throughout the rest of the pregnancy and the outcome. The age group 20–29 was selected in the first instance for study to exclude any possible influence of increased age of the mother (Fig. 2). There is a definite increase in the incidence of albuminuria later in pregnancy when the blood pressure is over 80 mm. at the 20th week of pregnancy, but the perinatal mortality and the prematurity rates are not affected. Similar results were obtained when all age groups were included in the analysis so that it seemed justifiable to include all cases in the subsequent analyses.

The next step was the correlation between the blood pressure changes resulting from pregnancy and the outcome of the pregnancy. After much trial and error it was found that the changes occurring between the 20th and 30th weeks were technically the easiest to handle and much the most important clinically, particularly since changes occurring before the 30th week will have, in most cases, preceded the onset of clinically recognizable signs such as oedema and albuminuria. Also, it is well recognized (Hamlin, 1952; Thomson and Billewicz, 1957) that the rate of weight gain between the 20th and 30th weeks gives some indication of the subsequent incidence of albuminuria. Analysis of the present series confirmed that primigravidae gaining 1·25 pounds/week or more between the 20th and 30th weeks had a high incidence of albuminuria later in pregnancy.

Further analysis showed that the greater the rise in blood pressures between the 20th and

TABLE I

Average Blood Pressures at 20th Week in 4,215 Primigravidae by Age

Age	Diastolic mm. Hg	Systolic mm. Hg
Under 20	75	122
20–24	75	124
25–29	75	125
30–34	77	125
35+	78	128

TABLE II

Influence of 20 Weeks Diastolic Blood Pressure and Change in Blood Pressure and Weight Gain Between 20–30 Weeks on the Incidence of Albuminuria

	20–30 Weeks Rise in Diastolic Blood Pressure					
	Less than 5 mm.			5 mm. or More		
20 weeks diastolic blood pressure:						
Less than 80 mm.	2·3	3·6	5·9	4·2	5·5	10·3
80 mm. or more	4·4	6·9	9·4	17·3	9·4	16·1
	<0·8	0·8–1·2	1·2+	<0·8	0·8–1·2	1·2+
	20–30 Weeks Average Weekly Weight Gain in Pounds					

30th weeks the higher the incidence of albuminuria and perinatal death. When the cases were divided into two groups depending on whether the diastolic blood pressure rose more or less than 5 mm. the difference in outcome was just as significant as when 10 mm. was used as the dividing line.

Thus the likelihood of albuminuria developing is increased when the 20th week diastolic blood pressure is 80 mm. or more, or when the 20th to 30th week blood pressure change is 5 mm. or more, or again when the 20th to 30th week weight gain is high (over 1·25 pounds/week).

An analysis of the combination of these three factors (Table II and Fig. 3) shows that, as expected, a high initial blood pressure, a high blood pressure rise and a high weight gain produces a high incidence of albuminuria, but,

FIG. 3

Influence of 20th week diastolic blood pressure and rise of diastolic blood pressure and weight gain between 20th and 30th weeks on the incidence of albuminuria.

rather unexpectedly, the incidence is equally great in the group characterized by a high initial pressure, high blood pressure rise but low weight gain. The lowest incidence of albuminuria occurred in the group with a low initial blood pressure, low blood pressure rise and low weight gain. The high initial blood pressure group has a low incidence of albuminuria provided that between the 20th and the 30th week there is little if any rise of blood pressure and a low weight gain.

As the initial blood pressure level at the 20th week does not influence the perinatal mortality or the prematurity rate, only the changes in blood pressure and weight between the 20th and 30th weeks were considered and it was found that the highest perinatal mortality rate occurred in the high blood pressure rise–low weight gain group and the lowest rate in the low blood pressure rise–moderate weight gain group (Table III). The high perinatal mortality in the high rise–low gain group is mainly due to prematurity (44 per cent) while in the high rise–high gain group it is mainly due to toxaemia (42 per cent).

The prematurity rate is not significantly affected by the rise in blood pressure from the 20th to the 30th weeks but is greatly influenced by the amount of weight gain (Table III).

Similar results were obtained when systolic blood pressure levels above and below 130 mm. at 20 weeks and a rise of more or less than 10 mm. between the 20th and 30th weeks were used.

TABLE III

Influence of Change in Blood Pressure and Weight Gain Between 20 and 30 Weeks on Perinatal Mortality and Prematurity Rates

	20–30 Weeks Rise in Diastolic Blood Pressure					
	Less than 5 mm.			5 mm. or More		
Perinatal mortality	18·7	17·8	28·8	49·3	39·4	31·5
Prematurity	19·3	11·5	9·0	21·4	14·2	10·9
	<0·8	0·8–1·2	1·2+	<0·8	0·8–1·2	1·2+
	20–30 Weeks Average Weekly Weight Gain in Pounds					

It is then possible to predict which combination of blood pressure levels, blood pressure changes and weight changes will be likely to lead to high or low incidences of albuminuria, perinatal mortality or prematurity. For example, the primigravida with the greatest risk of developing all three complications is the one with a 20th week blood pressure of 80 mm. or more, a high rise of blood pressure and a low weight gain between the 20th and 30th weeks.

It will be recalled that no attempt was made to limit weight increase by dietary control and that consequently the mortality and morbidity rates might be unnecessarily high. However, Thomson (1960) has found in a carefully controlled study that, while it was possible to prevent excessive weight gain by dieting, the benefit as measured by the fall in the incidence of albuminuria or perinatal mortality was small.

As the rise in blood pressure between the 20th and 30th week determines to some extent whether albuminuria develops later it may be that the amount of the rise of blood pressure is more important than the actual level reached. To examine this point the change in blood pressure between the 20th week and delivery has been related to the initial level of blood pressure and to the incidence of albuminuria (Table IV). A greater rise in blood pressure between 20 weeks and delivery occurs in those with low 20th week pressures than in those with higher pressures before a significant increase in the incidence of albuminuria occurs. The amount of rise necessary to produce albuminuria decreases steadily with increasing levels of 20th week blood pressures. This is strong evidence that it is the level reached rather than the amount of rise in blood pressure which is important. It is unlikely that there is a precise level which is critical and in any case the technique of blood pressure recording is too unreliable to measure it. Nevertheless a rise of diastolic blood pressure to over 90 mm. Hg could be regarded as an indication that "pre-eclampsia" had developed.

TABLE IV

Albuminuric Toxaemia Rates (per cent) by Rise of Diastolic Blood Pressure

Rise 20 Weeks to Delivery	Diastolic Blood Pressure at 20th Week			
	Under 70	70–79	80–89	90+
Under 10	1	1	3	8
10–14 ..	1	3	10	20
15–19 ..	3	6	16	
20–24 ..	4	19	30	
25+ ..	17	30	44	

When the blood pressure changes after the 30th week were considered it was found that the trends in blood pressure varied so much as almost to defy arrangement in a manageable number of groups. However, 3 groups were finally decided upon (Table V). The first group (Low) consisted of those in whom the diastolic blood pressure recording was under 90 mm. at 20, 30 and 36 weeks and again at the last antenatal examination prior to delivery or admission to hospital before delivery. The second group

TABLE V

Blood Pressure Changes During Pregnancy in:		
Low	Never above 90 mm.	2,608 (62%)
Labile	Occasionally above 90 mm. ..	842 (20%)
Rising	Steady rise to 90 mm. or more ..	765 (18%)

(Labile) consists of those in whom the blood pressure exceeded 90+ mm. intermittently without there being any indication of a steady rise between 20 weeks and delivery. The third group (Rising) consists of those in whom the blood pressure showed a steady upward trend, the last reading before delivery being in all cases more than 90 mm. The cases were also divided with reference to a critical level of systolic blood pressure of 140 mm. The results were very similar to those obtained using the diastolic pressure but were not quite so consistent.

The perinatal mortality and the incidence of albuminuria is highest in the Rising Group (Fig. 4, Table VI). In the Low Group not only was the overall incidence small but in all 40 cases in which albuminuria developed it

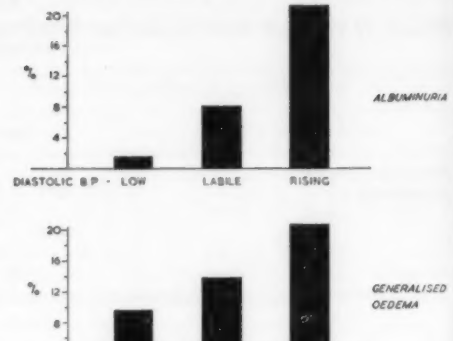

FIG. 4

Incidence of albuminuria, generalized oedema and perinatal mortality in the three blood pressure groups.

TABLE VI

Characteristics of the 3 Groups

		Low	Labile	Rising
Perinatal mortality (per mille)		22·6	19·0	57·5
Albuminuria (per cent)		1·5	8·1	21·3
Generalized oedema (per cent)		9·6	13·9	20·7
"Obesity"	Light	27·6	20·4	20·6
	Medium	51·9	46·2	48·2
	Heavy	20·5	33·4	31·2
		100%	100%	100%
Age	−25	62·8	61·5	56·3
	25–29	28·0	26·5	28·6
	30+	9·2	12·0	15·1
		100%	100%	100%
Weight gain, pounds/week	<0·75	29·5	22·3	19·1
	0·75–1·25	51·5	50·0	46·5
	1·25+	19·0	27·7	34·4
		100%	100%	100%

appeared in the urine for the first time just before or during labour.

The Labile and Rising Groups contained a relatively high proportion of heavy women when the cases were divided into light, medium and heavy for their height. This was done by taking a 25 : 50 : 25 division of the 20-week weight distributions at each inch of height. The Labile and Rising Groups also had a high proportion of women with a high weight gain in pregnancy and an excess of women over 30 years of age (Fig. 5, Table VI).

Various subdivisions of these 3 groups according to changes in blood pressure at different stages of pregnancy were examined and it was found that unless the increments are small throughout pregnancy a case which lands in the Rising Group is a worse risk than a case in any other group, both with regard to perinatal mortality and albuminuria. It was also found that, although there is a critical level, probably around 90 mm. diastolic pressure, for the development of albuminuria the cases having a higher 20 weeks to delivery rise have a greater incidence, although the death rate is only slightly increased.

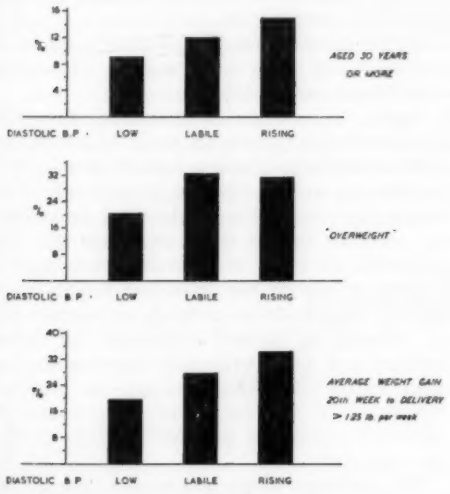

FIG. 5

Characteristics of the three blood pressure groups.

A fluctuating blood pressure (Labile Group) is not dangerous so far as the baby is concerned. In practice, however, when any individual blood pressure recording is high we are unable to say whether the blood pressure will remain elevated or not.

The selection of 90 mm. as the critical level of blood pressure is convenient in practice because in about 20 per cent of primigravidae the blood pressure rises up to and is maintained at or above this level. A lower limit would lead to the inclusion of too many cases where pregnancy remains uncomplicated, while a higher limit would lead to the exclusion of too many potentially complicated cases.

A systolic blood pressure of 140 mm. has also proved to be a useful dividing line between the normal and the abnormal.

Another aspect of morbidity which must be considered is the possible relationship of a raised blood pressure in a first pregnancy to its recurrence in any subsequent pregnancy.

The behaviour in their second pregnancies of the 3 groups previously described is shown in Table VII.

This indicates that women who were in the Low Group (−90 mm. all the time) in the first pregnancy are unlikely to show a rising pattern of blood pressure in the second pregnancy; that the majority of those in the Labile Group (fluctuating) fall into the Low Group in the second pregnancy and that half of those in the Rising Group also fall into the Low Group in the second pregnancy. Nevertheless about a quarter of them are to be found in the Rising Group again.

TABLE VII

Behaviour of Blood Pressure in the Three Groups in First and Second Pregnancies

Second Pregnancy	First Pregnancy		
	Low	Labile	Rising
Low	89	66	52
Labile	6	15	19
Rising	5	19	29
	100%	100%	100%

TABLE VIII

Incidence of Toxaemia in Successive Pregnancies of 128 Women

Pregnancy	No Toxaemia		Mild Toxaemia		Albuminuric Toxaemia	
	No.	%	No.	%	No.	%
First	95	74·2	27	21·1	6	4·7
Second	114	89·1	13	10·2	1	0·8
Third	118	92·2	9	7·0	1	0·8
Fourth	111	86·7	17	13·3	—	—

To see how the initial blood pressure in the second pregnancy compares with the initial pressure in the first, the readings at 20 weeks have been compared in 433 sample cases in which detailed blood pressure readings were available for both pregnancies. Whether or not albuminuria occurred in the first pregnancy, the 20th week blood pressure was practically identical in both pregnancies. In the cases where albuminuria occurred in the first pregnancy the pressure both in the first and the second pregnancy tended to be higher (average 78 mm.) than in those where albuminuria did not occur in the first pregnancy (average 76 mm.).

The result of this investigation therefore seems to confirm the usefulness of Nelson's (1955) classification of pre-eclampsia, in which the diagnosis of mild pre-eclamptic toxaemia was made when the diastolic blood pressure rises to 90 mm. Hg or more on two occasions separated by a day after the 26th week of pregnancy. In the severe variety there is in addition 0·25 g. protein per litre or more in the urine. Oedema is not used in this classification as it is difficult to measure with any precision. Thus the severity of the condition is determined more by the degree of proteinuria than by the rise of blood pressure.

Caution has to be exercised in carrying the study of hypertension in subsequent pregnancies beyond the second since in our area at least many of those having a 3rd or 4th baby are delivered under the domiciliary scheme. Since 1953, by arrangement with midwives, general practitioners and consultants, antenatal records of all Aberdeen domiciliary births as well as hospital births have been made available for analysis.

The most exact method of studying this problem is to follow a cohort of women through each successive pregnancy. The blood pressure readings in 128 women have been studied in each of four pregnancies and the results are shown in Table VIII. The incidence of albuminuric toxaemia (severe pre-eclampsia) in second pregnancies is only one-sixth of this for first pregnancies and there is no change in the incidence in the third and fourth pregnancies (Table VII). The incidence of mild pre-eclampsia in second pregnancies is half that in the first and the incidence remains unchanged in third and fourth pregnancies.

As the numbers were small a cross-sectional analysis using much larger number of women was carried out (Table IX).

Again, the incidence of albuminuric toxaemia in the second pregnancy fell to about a fifth and mild toxaemia to about a half of that in first pregnancies and remained at about this level in succeeding pregnancies. If hospital cases only are used for such a study one finds that the incidence of mild and severe pre-eclampsia appears to rise in the third and fourth pregnancies. This is almost certainly an artefact due to selection of normal multiparae for home delivery and those with such abnormalities as hypertension for hospital delivery—an excellent illustration of the danger of being misled in statistical analysis if possible selection factors are neglected.

The incidence of pre-eclampsia in the second pregnancy can be accepted then as representative of all subsequent pregnancies. I have previously

TABLE IX

Incidence of Toxaemia in All Parities

Pregnancy		No Toxaemia	Mild Toxaemia	Albuminuric Toxaemia
First	(5,214)	71·4	24·1	5·5
Second	(4,445)	86·1	12·5	1·4
Third	(2,726)	88·8	9·9	1·3
Four or more	(3,060)	88·6	10·2	1·2

shown (MacGillivray, 1958) that the incidence of toxaemia in a second pregnancy is very low if the first pregnancy was normotensive but the fall is not so marked if there was toxaemia in the first pregnancy. A previous abortion reduces the incidence but not so much as a viable pregnancy. A twin pregnancy markedly increases the incidence even though there has been a previous normotensive pregnancy.

The outcome of the second pregnancy in those who had a perinatal death directly attributable to pre-eclamptic toxaemia was also studied. There were 52 booked primigravidae in 1938–57 who had lost their first babies as a result of pre-eclampsia and for whom details of the second pregnancy were available. The recurrence of albuminuric toxaemia (severe pre-eclampsia) in a second pregnancy was three times as great as in comparable cases of pre-eclampsia where the first baby survived.

Five of the 9 cases with recurrence of severe pre-eclampsia occurred in women below 20 years. Their blood pressures at about the 20th week of the 1st pregnancy were 140/94, 142/96, 140/78, 150/90 and 130/90. It thus appears to be young women who are hypertensive early in pregnancy who are more prone to have a recurrence of severe toxaemia.

I wish now to turn to the consideration of the late effect of pre-eclampsia on the blood pressure. Four groups of women who were between 35 and 50 years were selected for this study; (*a*) those who had had albuminuric toxaemia in a first pregnancy; (*b*) those who had had mild toxaemia; (*c*) those who were normotensive; and (*d*) those who had not had a pregnancy. This last group of nulliparae was composed of factory and office workers, school teachers, shop assistants and housewives. The results are shown in Table X.

It is clear that the lowest incidence of hypertension occurred in the women who had been normotensive during the first pregnancy while the highest was found in those who had mild toxaemia—distinctly higher than those who had had albuminuric toxaemia.

If toxaemia causes hypertension later in life then the nulliparous women should have the same level of blood pressure as the parous women who had been normotensive in pregnancy, but in fact the incidence of hypertension in the nulliparous women is distinctly greater

TABLE X

Hypertension in Women Aged 35–50 Years

Previous History		Diastolic Over 90 mm.	Systolic Over 140 mm.	Mean Age
		%	%	Years
Nulliparae	(197)	35	41	45
Parous women:				
No toxaemia	(185)	21	26	42
Mild toxaemia	(96)	60	58	42
Albuminuric toxaemia	(53)	40	43	43

than that and is in fact about the same as the average for all parous women. This strongly supports Browne and Sheumack's (1956) and Dieckmann's (1952) hypothesis that there is a hypertensive tendency in some women which becomes manifest in pregnancy and produces what we usually call mild pre-eclampsia. These same people develop hypertension later in life. In addition the incidence of permanent hypertension in women who had albuminuric toxaemia in the first pregnancy is less than in those who had mild toxaemia. These facts suggest that the practice of carrying on pregnancy in a case of severe toxaemia till the child is viable is unlikely to increase the risk of permanent hypertension.

On this basis many of the cases of mild toxaemia are more likely to be due to the effect of pregnancy on women with hypertensive tendencies whereas when albuminuria occurs the explanation is more likely to be the result of some pathological response to pregnancy. This would fit in with the fact that in later life the women who have had "mild toxaemia" have higher blood pressures than those who have had albuminuric toxaemia. Even if such a distinction is sound and justifiable it is most unlikely that there is a clear-cut division between the two groups.

The epidemiology of hypertension without proteinuria has several characteristic features which suggest that it should not always be regarded as mild toxaemia. Its incidence is not so greatly reduced in a second compared with a first pregnancy; obesity is much more clearly associated with it than with albuminuric toxaemia; mild hypertension occurring during late pregnancy has no depressive effect on foetal growth (Baird, Thomson and Billewicz, 1957); the incidence is higher in primigravidae over the age of 30 and it does not raise foetal mortality (Nelson, 1955); hypertension in later life is more common in women who had hypertension only during pregnancy than in those who had albuminuric toxaemia.

Hypertension is known to be an inherited trait so that it might be possible to investigate this possibility of albuminuric toxaemia being different from mild toxaemia by studying the incidence of mild and albuminuric toxaemia in sisters. The records of the 555 sisters of 99 primigravidae with mild toxaemia, 47 with albuminuric toxaemia, and 273 who had no toxaemia, were scrutinized for evidence of toxaemia and the results are shown in Figure 6 and Table XI.

There is a higher incidence of toxaemia in the sisters of those primigravidae who had toxaemia and the severity of the toxaemia is to some extent a familial tendency. Unfortunately this does not help in determining whether mild toxaemia is a different disease from albuminuric toxaemia.

If mild pre-eclampsia is more often a manifestation of a hypertensive tendency than is the case with severe pre-eclampsia then it seems justifiable to postulate some factor in the pregnancy itself which produces the disease syndrome which we call severe pre-eclampsia. This factor or "toxin" is most active in a first pregnancy and has relatively little effect in a later pregnancy, suggesting almost that the body had acquired an immunity to it.

It is impossible at present to determine precisely how far the condition which we call pre-eclampsia is a mixture of conditions, one a hypertensive tendency and the other a toxin or maladjustment to a first pregnancy, but the evidence presented here strongly suggests this possibility. This could account for much of the confusion which exists about this disease.

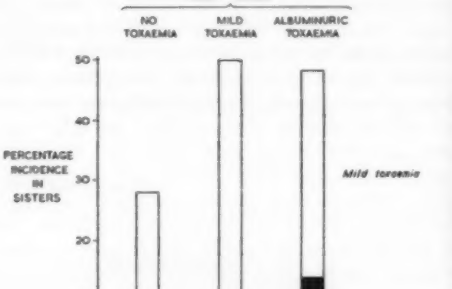

FIG. 6
Incidence of toxaemia in sisters.

TABLE XI

Percentage Incidence of Toxaemia in the First Pregnancies of Sisters of Primigravidae With or Without Toxaemia

			Index Cases		
			No Toxaemia (273)	Mild Toxaemia (99)	Albuminuric Toxaemia (47)
Sisters	No toxaemia	(362)	71·8	50·8	51·7
	Mild toxaemia	(157)	23·8	40·0	34·5
	Albuminuric toxaemia	(36)	4·4	9·2	13·8
			100%	100%	100%

(Numbers of cases in brackets)

Although it is not possible to make a clear-cut distinction between pregnancy hypertension and albuminuric toxaemia nor to single out the women who will develop toxaemia, nevertheless this investigation has picked out high risk groups by the 30th week of pregnancy in many cases.

A more rational plan of antenatal care in the early detection of pre-eclampsia than at present in common use can therefore be evolved. In ideal circumstances, of course, frequent examinations throughout pregnancy would be the aim but this is costly in terms of time and energy.

The standard practice is to examine all patients at monthly intervals until 30 weeks; every 2 or 3 weeks from then until 36 weeks, and thereafter every week until delivery.

The most severe cases of pre-eclamptic toxaemia and those most difficult to treat satisfactorily develop between about 30 and 36 weeks. The more frequent the examinations at this time the less the delay in diagnosis when signs and symptoms develop. Frequent examination of all patients from the 30th week onwards would increase unduly the work of antenatal clinics but this could be avoided if the high risk cases were seen more frequently and the low risk cases less frequently.

The low risk primigravida is characterized by a diastolic blood pressure at 20 weeks of less than 80 mm. or a systolic pressure of less than 130 mm., a rise of diastolic blood pressure of less than 5 mm., or systolic pressure of less than 10 mm. between 20 and 30 weeks, an average weekly weight gain at this time of between 0·75 and 1·25 pounds. It is preferable that the average of the blood pressures around 20 and 30 weeks should be used.

Multiparae in whom no rise of blood pressure has occurred in previous pregnancies almost invariably fall into the low risk category.

All other pregnancies fall into the high risk category. A fluctuating blood pressure is of less significance than one showing a steady rise to 90 mm. or more. Obesity and increasing age are additional risks. A family history of pre-eclampsia is an additional reason for classifying a woman in the high risk category.

Having thus classified the patients at 30 weeks the high risk group can be seen weekly and the others less often as circumstances demand. Such a re-distribution of antenatal care would not increase the overall work.

SUMMARY AND CONCLUSIONS

In this blood pressure analysis of a total population it has been shown that the level of blood pressure at the 20th week of pregnancy is similar to that in non-pregnant females of the same age. The blood pressure level thereafter may and often does change, and this study was carried out to try to determine which level of blood pressure or rise in blood pressure in pregnancy could be considered abnormal.

The criteria of abnormality selected were albuminuria, perinatal mortality and pre-

maturity. The incidence of neither perinatal mortality nor prematurity is influenced by the level of blood pressure at 20 weeks, but the incidence of albuminuria developing in late pregnancy increases when the diastolic blood pressure is 80 mm. Hg or more, or the systolic pressure is 130 mm. or more at 20 weeks.

A rise of 5 mm. or more diastolic or 10 mm. or more systolic pressure between the 20th and 30th weeks causes an increase in the incidence of albuminuria and perinatal mortality, but not of prematurity, which, however, like albuminuria is influenced by the weight gain between the 20th and 30th weeks.

By using a combination of 20th week blood pressure level, and blood pressure rise and weight gain between the 20th and 30th weeks it is possible to predict the primigravidae with the greatest liability to albuminuria, perinatal death or prematurity. This information can be utilized in planning antenatal care.

The level of blood pressure attained in late pregnancy is more important than the amount of rise in pregnancy so far as the development of albuminuria is concerned and the critical level is about 90 mm. Hg diastolic or 140 mm. Hg systolic. Analysis following division of the cases into Low, Labile and Rising Groups with reference to a diastolic pressure of 90 mm. furnished evidence that these levels should be considered critical. Nelson's (1955) classification of pre-eclampsia appears from this analysis to be a reasonable one to adopt.

The incidence of pre-eclamptic toxaemia, according to this definition, fell in second pregnancies and remained low in succeeding pregnancies. Albuminuric toxaemia fell to about a fifth while mild toxaemia fell to a half.

Women who have had toxaemia in a first pregnancy are more liable to develop toxaemia in subsequent pregnancies than those who had no toxaemia in a first pregnancy and recurrence of severe toxaemia is more likely tc occur in young women who have high blood pressure early in their first pregnancies.

An early abortion in a first pregnancy reduces the incidence of albuminuria in the subsequent pregnancy to one-third of that in first pregnancies which continue to viability. This, together with changes which have been shown to occur between the 20th and 30th weeks, suggests that the clue to the aetiology of pre-eclamptic toxaemia should be sought in early pregnancy.

Hypertension in later life is as common in nulliparous women as in women who had albuminuric toxaemia, but the incidence is higher in women who had mild toxaemia. This, together with other facts, is considered good evidence for believing that some women diagnosed as having mild pre-eclampsia have in fact a hypertensive tendency which manifests itself during pregnancy but does not necessarily affect the pregnancy adversely. Unfortunately we have no means, at present, of distinguishing this hypertensive manifestation from true mild pre-eclampsia.

A comparison of the sisters of women with and without pre-eclamptic toxaemia revealed that there is a familial tendency to this disease which may be independent of any hypertensive familial trait.

To the clinician this study gives precision to what have possibly been clinical impressions. To the research worker the value of this information is in indicating which patients should be selected for study, not only of the established condition but also of those most likely to develop the disease and also at what period in pregnancy investigations should be carried out.

It is often impossible to compare the results of different workers because either no definition of pre-eclampsia is given or the definitions used vary widely. At least, it can be concluded from this study that results of investigations in women with hypertension only in late pregnancy should be considered separately from those in women who have albuminuric toxaemia and that as far as possible investigations should be limited to primigravidae.

With the realization that there are almost certainly two components to what is commonly called mild pre-eclampsia, confusion arising from this can be avoided.

Although the actual cause of pre-eclampsia may not be determined by epidemiological studies, at least it can be said that further lines of investigation by other methods are revealed and any theory which is propounded must fit the facts disclosed by this study.

I wish to acknowledge my indebtedness to Professor Sir Dugald Baird and my colleagues in the M.R.C. Obstetric Medicine Research Unit, Aberdeen, for their help in the preparation of this lecture; in particular to Mr. W. Z. Billewicz for statistical analysis and Dr. Eleanor M. Adams for much of the field work.

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PERIPLACENTAL HAEMORRHAGE, FOETAL DEATH AND LESIONS OF THE KIDNEY AND OTHER VISCERA IN PREGNANT RATS RECEIVING PROGESTERONE

1.—The Uterus and Placenta

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IN preliminary communications (1960b, c) I stated that the giving of progesterone to rats late in pregnancy may be followed by periplacental haemorrhage, intra-uterine death of the foetus, and by renal and liver necrosis. Two factors appeared to be important in the production of these lesions, the precise time of gestation at which the injections of progesterone were given and the type of diet taken during pregnancy.

There was some suggestion that a greater incidence of lesions occurred in those animals fed a choline deficient diet or a choline deficient diet plus 0·5 per cent choline chloride than in those fed normal rat meal. The results, however, were complicated by the fact that the response of the animal to progesterone might also differ according to the time of gestation at which the injections were given. Unfortunately in the earlier work this time was not known precisely and no firm conclusions were reached.

Later it became clear that, whereas the experimental diet has no influence on the incidence of uterine lesions, the period of gestation at which the injections are given is a most important factor. On the other hand both factors, diet as well as the time of gestation, seem to influence the incidence of lesions in the kidney and liver.

The present paper however is concerned mainly with the uterine lesions, and the discussion of the other viscera is left over for a further report.

MATERIAL AND METHODS

Rats of the Wistar Albino strain were used throughout. At mating their weight varied between 115 and 195 grammes with over 80 per cent within the range 120 to 160 grammes. All pregnant rats were virgin before mating.

Diet: Three diets were used: (*a*) a choline free diet known to produce renal cortical necrosis in male and female weanling rats (Moore, 1957, 1959), although neither renal nor uterine lesions in the young pregnant rat (Moore, 1960a); (*b*) a choline free diet plus added 0·5 per cent choline chloride and (*c*) normal rat meal (Medical Research Council Formula).

The time of mating was determined by the finding of sperms in the vaginal smear. The day on which sperms were found was counted as Day 1. After mating, females were placed in individual cages and given one of the three diets. A total of 20 milligrammes of progesterone was given intramuscularly in 4 daily doses of 5 milligrammes each, the day of commencement of the injections being between the 16th and the 20th day of gestation. Sixty-two pregnant animals were used.

The animals were weighed weekly until the last few days of pregnancy when most were weighed daily until delivery or autopsy. Antepartum haemorrhage was very carefully sought for and the animals left in the laboratory under constant supervision, at least during the day. All organs were observed at autopsy but histological examination was only carried out

on the liver, kidney and on the uterus with its contents. The attached placenta was bisected and one block taken. Routine staining methods were used but in addition all sections of uteri with placenta *in situ* were stained with Osgood and Washbourn's modification of Pickworth's stain, in order to demonstrate small amounts of blood in the uterine cavity.

The majority of the animals were killed either after delivery at the normal time on the 22nd or 23rd day or, in those that remained undelivered due to the progesterone administration (Reynolds, 1949, p. 121), between the 24th and 26th days of gestation. A few animals in each group were killed during delivery. The foetuses which were alive at delivery were fostered. Foetuses, whether alive or dead, which were undelivered at the time of maternal death were fixed *in utero* so as to preserve the utero-placental relationship. After fixation of the uterus the foetuses were removed but not investigated further.

Thirty-one non-pregnant animals on the different diets were given progesterone in the same dosage and allowed to survive for the same period as the pregnant animals. Twenty-five were autopsied and no lesions were found in the kidney and liver. Six animals were allowed to survive. In these the blood urea was measured at intervals and since no rise was found it is assumed that renal lesions did not occur.

Results

The changes within the uterus fall into 3 groups: (*a*) No lesions—in which pregnancy and parturition are normal although delivery may be delayed beyond the normal time. (*b*) Intra-uterine foetal death. (*c*) Intra-uterine haemorrhage with foetal death. In the last group the haemorrhage may be manifest clinically as ante-partum bleeding or may be seen at autopsy in some or all of the ampullae (Fig. 2).

The full data of the incidence of these groups and their distribution according to diet and the time of gestation at which injections commenced is given in Table I. The most important fact is

TABLE I

The Incidence and Type of Uterine Lesion in Pregnant Rats Fed Different Diets and Receiving Progesterone

Gestation Days when Progesterone Given	Number of Animals on Each of Diets		Type of Uterine Response: No Lesion		Intra-uterine Foetal Death		Intra-uterine Haemorrhage and Foetal Death	
16 to 19	Choline deficient	5	5		0		0	
	Choline deficient with choline chloride	3 } 11	2 } 10		0 } 0		1 } 1	
	Rat meal	3	3		0		0	
17 to 20	Choline deficient	6	4		0		2	
	Choline deficient with choline chloride	2 } 10	2 } 8		0 } 0		0 } 2	
	Rat meal	2	2		0		0	
18 to 21	Choline deficient	5	1		2		2	
	Choline deficient with choline chloride	5 } 14	1 } 5		3 } 6		1 } 3	
	Rat meal	4	3		1		0	
19 to 22	Choline deficient	5	0		1		4	
	Choline deficient with choline chloride	4 } 13	1 } 2		2 } 4		1 } 7	
	Rat meal	4	1		1		2	
20 to 23	Choline deficient	5	0		1		4	
	Choline deficient with choline chloride	4 } 14	0 } 0		3 } 6		1 } 8	
	Rat meal	5	0		2		3	

that the incidence of abnormalities within the uterus increases the later in pregnancy the progesterone injections are started—from 10 per cent in those receiving injections from the 16th to the 19th day of gestation to 100 per cent in those starting on the 20th day and ending on the 23rd day. The test diets had no consistent effect on the incidence nor severity of these uterine lesions.

Ante-partum effects: In both abnormal groups those animals, which were shown ultimately to have uterine lesions, became ill during the period following the injections. The animals commencing injections on the 17th, 18th, 19th and 20th days of gestation showed symptoms between the 19th and 24th days of gestation. In over 90 per cent the illness occurred between the 22nd and 24th days of gestation and there was no obvious relationship between the time of this occurrence and the time of commencing injections.

The most dramatic symptom is that of ante-partum haemorrhage which defines the second abnormal group. The animals may be ill and lethargic with or without haemorrhage. Hiccoughs occur in the severely ill.

Foetal death: In both abnormal groups the foetuses remaining undelivered on the 25th day of gestation are dead and usually macerated. In those animals examined on the 23rd and 24th days the whole litter may be dead or some foetuses may remain alive. No animal was examined earlier than the 23rd day unless aborting. It is probable therefore that the foetuses die as a rule during the 23rd and 24th days. There is insufficient data to detect any differences between the various injection groups.

Three animals, in which injections were commenced on the 18th, 19th and 20th days, were examined at laparotomy either on the 23rd or 24th day. At this time all the foetuses were alive, but at autopsy 1 day later were dead. This fact not only supports the estimated time of death but suggests that it is not intimately related to the time of commencement of the injections.

Intra-uterine haemorrhage: In those animals with intra-uterine haemorrhage the naked eye appearances of the uterus are characteristic. There are widespread blotches of haemorrhage with the greatest concentration of blood surrounding the placenta like a ring (Fig. 2). In the individual animal some ampullae may and some may not have the lesion. Similarly one horn may show the lesions and the other horn be unaffected. In section the blood is seen to be present within the uterine cavity lying between the uterine epithelium and the foetal membranes (Fig. 3). The greatest accumulation is at the angle between the uterus and the placenta. In a few ampullae a continuation of haemorrhage, with partial separation of the placenta, can be demonstrated between a maternal blood vessel and the blood in the uterine cavity.

Placental lesions: There are no discernible histological differences between the two abnormal groups and the lesions are discussed together.

On the 23rd day of gestation only one animal is available for study. It commenced injections on the 20th day. The placentas—7 in all—did not differ in any way from the normal. On the 24th and 25th days 138 placentas from 35 animals are available. The important change at this time is necrosis of the labyrinth. Two types are found, complete and focal. Total necrosis is found only in those placentas which are completely separated from the uterine wall. The converse is not true however and a placenta may be wholly separate and yet not show necrosis. It may be concluded that total necrosis of the labyrinth and junctional zone follows complete separation of the placenta.

Focal necrosis of the labyrinth tissues may be found in attached placentas as well as those showing some degree of separation. The necrosis involves the trophoblast as well as foetal capillaries, occurs most commonly just beneath the junctional zone and may extend deep into the labyrinth. Focal collections of cytotrophoblast are not prominent in the normal at the time of delivery but they seem not less in these animals and have not been observed to be necrotic. The necrotic area is heavily surrounded and infiltrated with polymorphonuclear leucocytes, present in both the maternal sinuses and foetal capillaries. The degree of this infiltration is very much greater than the slight polymorph infiltration which occurs in the normal placenta

FIG. 1

Normal pregnant uterus of the rat at the time of delivery.

FIG. 2

Intra-uterine haemorrhages at the 25th day of gestation in a rat commencing progesterone on the 20th day.

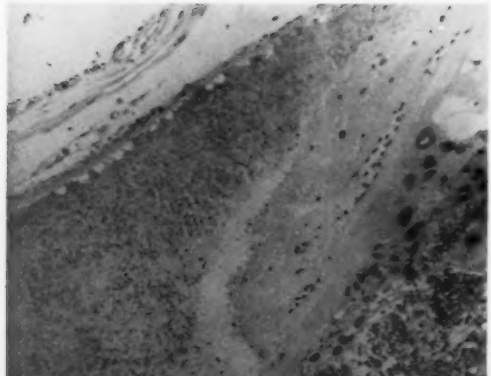

FIG. 3

Section to show intra-uterine haemorrhage lying between the uterine wall and the placental labyrinth. H. & E. ×94.

at the time of delivery. Fibrin is not present. The junctional trophoblast tissues of the attached placenta are not different from the normal at the time of delivery.

Other visceral lesions: All the animals receiving a choline deficient diet showed the characteristic fatty change in the liver. This has, according to a previous report (Moore, 1960a) no effect on pregnancy.

Of considerably more importance is the fact that 3 animals out of the 18 fed either a choline deficient diet or a choline deficient diet plus 0·5 grammes per cent choline chloride, and injected with progesterone on the 19th and 20th days of pregnancy, sustained a necrosis of the kidney, or liver, or both. All 3 animals had uterine lesions. The liver lesion is a centrolobular necrosis and the kidney is either a renal cortical necrosis of confluent focal type (Sheehan and Moore, 1952, p. 105) or a necrosis of proximal convoluted tubules. Symeonidis (1949) described similar renal lesions.

The incidence of renal and liver lesions is low but from other data previously published or from further unpublished experiments it may be tentatively stated that the incidence of renal lesions increases with the increase of uterine lesions, that the incidence of renal lesions is confined to those groups receiving injections on the 19th and 20th days of gestation, and finally that the incidence is greater amongst those animals receiving the experimental diets than in those receiving normal rat meal. A full report of the renal pathology must wait on further experiments. Nevertheless that the lesions occur may be of importance in the discussion of the uterine lesions and this is referred to later.

Discussion

Placental Necrosis

There is little doubt that 3 of the 4 major uterine effects in pregnant rats described here —uterine haemorrhage, foetal death and an inhibition of parturition are due, directly or indirectly, to progesterone. The relationship, however, between progesterone administration and focal necrosis of the placental labyrinth is not completely clear but, since such focal necrosis does not occur at 23-days gestation, whereas it is quite common on the 24th and 25th days, it is probable that the necrosis is a result of the delay of parturition rather than as a direct result of progesterone itself.

One hypothesis to explain the pregnant rat's response to progesterone hinges on this lesion of placental necrosis. Symeonidis (1949), in experiments of this type, reported the occurrence of ante-partum haemorrhage, foetal death, renal and liver necrosis and placental necrosis. In the placenta he described degeneration and necrosis of the cellular chorionic elements with disappearance of the Langhans' cell; from his illustrations the necrosis would appear to be at the junctional zone. He regarded these changes as abnormal and suggested that possibly all the results of progesterone administration were due to toxic substances released from the necrotic placenta. The results here do not support this idea. Necrosis of the junctional syncytiotrophoblast is within normal limits and the cytotrophoblast is not abnormally diminished and is not seen to be necrotic. Focal labyrinth necrosis is admittedly abnormal and, whether or not it is due to progesterone, it is inconstant and may not be present even though the foetuses are dead and intra-uterine haemorrhage is present. It is concluded therefore that foetal death and intra-uterine haemorrhage arise independently of placental necrosis.

Foetal Death

That foetal death may follow progesterone administration is somewhat controversial. Klein (1937), Heckel and Allen (1938) and Ehrhardt and Koenig (1939) appear to be the first authors to emphasize that progesterone itself might have an adverse effect on the foetus. Klein gave progesterone to normal rabbits between the 15th and 22nd day of pregnancy and found that a number of foetuses died. Heckel and Allen seem to associate such deaths with the prolongation of gestation; they stated that in the rabbit foetal death may occur if pregnancy is continued beyond the usual limit of 31 days up to the 35th day. On the other hand Ehrhardt and Koenig hold the view that progesterone given in high dosage to pregnant mice kills the foetuses by a direct action.

In all these reports, however, there is agree-

ment that the foetal death is due in some way to progesterone. Not all authorities have agreed with this in the past. Courrier (1945), discussing this work (p. 260 and 261), attributed the toxic action to impurities in the progesterone and stated that pure progesterone had no effect on the foetus. It is possible that in this work and in many others where pregnant rats have not suffered ill effects following progesterone administration, the explanation lies in the phenomenon of differing sensitivity of the animal according to the period of gestation, e.g., in Courrier's experiments on the rabbit no injections were given after the 22nd day of gestation.

A detailed examination of the foetuses has not been carried out in the present experiments and the cause of death is unknown. Foetal death can occur with the placenta *in situ* and without any apparent uterine abnormality as was first pointed out by Snyder (1934). Nor is it possible to agree that foetal death is related to the prolonged delay of parturition, as stated by Heckel and Allen (1938) and later by Wislocki (1956, p. 112). The evidence presented here indicates that the foetus dies before parturition can be said to be unduly delayed.

The view that progesterone kills the foetuses by a direct toxic action is supported by Karnofsky *et al.* (1952). They reported that the newborn mouse is killed by progesterone during the first day, but that in the following 2 or 3 days resistance develops rapidly. No histological details are given and no precise explanation is offered for the effect of progesterone. The cause of foetal death therefore must remain doubtful although there is nothing in the present work to invalidate the idea of a direct toxic action.

Intra-uterine Haemorrhage

In most earlier work little notice is taken of intra-uterine haemorrhage. Snyder (1934) and Hoopes (1934) mentioned casually that vaginal haemorrhage may occur but Symeonidis (1949), in the paper already referred to, seems to be the first to report in detail on the lesion of what he called periplacental haemorrhage. This lesion occurred when he gave progesterone to pregnant rats from the 15th to 18th days of gestation. The rats remained normal if the injections were given before the 15th day. Karnofsky *et al.* (1952) confirmed the findings in the mouse. On the other hand, Hester, Richardson and McKee (1953) repeated Symeonidis' work but failed to confirm the results. They suggested that the different strain of rat used was the probable explanation of the discrepancy. It would appear however that the times of injection differed in the two series and this could well explain the different results.

The cause of the haemorrhage is not clear although its source would appear to be wholly or partly maternal. In the absence of an organic placental or uterine lesion the failure of the normal haemostatic mechanism at about the time of delivery might be regarded as a failure of uterine tone and contractility. Another mechanism of haemostasis, however, is suggested by the finding of vascular sphincters of the uterine arteries in the mouse (Knisely, 1934). In this animal special contractile segments are found near the entrance of a branch of the uterine artery into the uterine wall and Knisely stated that they controlled the volume of blood supplied to the placental site at parturition. The mechanism is so effective that "free blood is hardly ever seen in the uterine lumen".

In the present experiments the prolonged relaxation of the uterus which may occur under progesterone administration is not invariably accompanied by intra-uterine haemorrhage. It is not unreasonable to suggest, therefore, that a mechanism of haemostasis similar to that of the mouse may also be found in the rat. On this assumption the cause of intra-uterine haemorrhage could be due to a direct effect of progesterone on the vascular sphincters of the vessels supplying each placental site, so that an inco-ordination is produced between uterine contraction and the vascular supply.

Similarly, a direct effect of progesterone on the renal vessels could explain the occurrence of renal cortical necrosis; this lesion may arise independently of the uterine disturbance (Moore, 1960b) and, by comparison with renal cortical necrosis in the human (Sheehan and Moore, 1952), may be presumed to be due to vasospasm.

Although this idea of the origin of the intra-uterine haemorrhage is quite hypothetical it nevertheless raises the possibility that foetal

death, too, might result from a vascular cause, i.e., uterine ischaemia.

Whatever may be the mechanism of the action of progesterone, the animal would appear to possess two factors which regulate its effects in these experiments. There is a general factor which determines the sensitivity of the animal according to the period of gestation, both as regards the renal lesions as well as those within the uterus. The second factor resides in the uterus itself; each ampulla may behave differently from its neighbours. The nature of these two factors is unknown. Since, however, many if not all of the lesions occur around the 23rd to 24th day, i.e., either within the normal delivery time or shortly afterwards, it is possible to speculate that the response to progesterone is linked in some way with the mechanism of parturition, particularly on the interactions of progesterone and the posterior pituitary hormones since it has been shown (Byrom and Pratt, 1959) that oxytocin assumes vasoconstrictor properties in the presence of ovarian activity and can in such circumstances provoke renal cortical necrosis.

Finally, as far as clinical medicine is concerned two points need to be made. Firstly, the association, in these experiments, of renal cortical necrosis, placental haemorrhage and foetal death is reminiscent of human abruptio placentae. Although this similarity is of considerable interest there is no evidence as yet to connect the present experimental findings with those of the human condition. Secondly, progesterone has been used clinically to inhibit premature delivery when this is threatened. There are good experimental grounds for this approach but it should be remembered from the same experimental work that progesterone may also cause foetal death.

Summary

When progesterone is given to rats late in pregnancy it is followed by intra-uterine haemorrhage and intra-uterine death of the foetuses. The incidence of these lesions rises sharply the later in pregnancy the injections are given, from 10 per cent when progesterone is given over 4 days from the 16th to the 19th day of gestation to 100 per cent when progesterone is given from the 20th to the 23rd days of gestation. A focal necrosis of the placental labyrinth may be found but it is inconstant and is not related to the occurrence of the other lesions.

In a small proportion of the same animals renal cortical necrosis and/or liver necrosis also occur.

Animals were fed one of three diets: choline free, choline free plus 0·5 grammes per cent choline chloride and normal rat meal. The experimental diets did not influence the incidence nor the severity of the uterine lesions.

The cause of foetal death remains unknown. It is not due to haemorrhage nor is it due to an undue delay of parturition.

Intra-uterine haemorrhage is probably wholly maternal in origin. In the absence of significant organic damage to the maternal and foetal placenta it is suggested that the haemorrhage is a result of the action of progesterone on sphincters of the uterine arteries with failure of the normal correlation with myometrial contractility.

The pregnant animal, however, would seem to possess two factors which modify the pathological effects of progesterone—a general factor responsible for the increase of sensitivity with duration of gestation and an ampullary factor which affects the response of each foetus and its placenta.

The resemblance of the present experimental findings with human abruptio placentae is noted.

Acknowledgments

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CAESAREAN SECTION—A LETHAL OPERATION?*

BY

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IN those days of the 1750s when Mr. Shandy senior gave curtain lectures to Mrs. Shandy on the advantages of Caesarean section, without in any way convincing her, the maternal mortality of the operation approached 100 per cent. Even a century later (1865) Radford, quoted by J. H. Young, reported from Great Britain 11 survivals only from 77 operations, a mortality corresponding to about 86 per cent.

The figures that I shall give during this address, and I cannot stress this too strongly, relate to that composite country lying to the south of Scotland, and known to our Registrar-General as England-and-Wales. I do not assert that any conclusions I may draw necessarily apply to Scotland, though perhaps it would not be altogether surprising if they did.

Some years ago it struck me as an assessor of maternal deaths that Caesarean section figured too frequently in the case records of patients dying in childbirth. At my instance the *Report on Confidential Enquiries into Maternal Deaths in England and Wales 1952–54* (Ministry of Health, 1957) included a chapter on Caesarean section, and the recently published report for 1955–57 (Ministry of Health, 1960) also contains one. In the first three years the Registrar-General recorded 1,812 deaths as due to or associated with childbirth, and 1,410 confidential reports were obtained for that period, i.e., from just over three-quarters of the cases. In 1955–57 there were 1,480 deaths in similar categories, and 1,200 reports were obtained, a rather greater proportion. In the first series 183 of the deaths reported were associated with but not necessarily due to Caesarean section, or 13 per cent. If ectopic gestation, abortion, and undelivered mothers are excluded, the ratio is 19·4 per cent, or nearly one-fifth of all the cases. In the 1955–57 report 184 of the deaths reported were associated with Caesarean section, or 15 per cent. If ectopic gestation, abortion, etc., are excluded the proportion rises to 23·8 per cent, or nearly one-quarter of the total. As the preface to the 1952–54 Report states: "Outstanding features of the report are . . . the untoward results of Caesarean section in some cases."

It is very probable that many of the patients who died after Caesarean section were correctly treated and would have succumbed whatever their treatment had been. It is possible to work out roughly the mortality from section over the countries concerned, and in their two reports the Ministry of Health has made some attempt to do this. I appreciate, as I am sure you do, that it is not justifiable to say, on considering the 1955–57 figures, that the mortality from Caesarean section being 3·5 per 1,000, a minimum estimate according to this later report, and the overall maternal mortality (including associated cases, but excluding abortions and ectopic gestations) being only 0·57 per 1,000, it is therefore much safer for a mother to be delivered vaginally. In many individual cases the risk is lower from Caesarean section; indeed, the best of all possible reasons for doing Caesarean section on Mrs. X. is that we *think* we are reducing the risk to her by doing so. This is a matter of opinion. We have no controls,

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and our decisions are likely to vary with our past experience and our temperaments.

It is, however, desirable that we should realize that by deciding on Caesarean section for Mrs. X., while we are reducing certain dangers, we are introducing or increasing others either inevitably or if we happen to be insufficiently skilled or experienced.

It is possible to produce series of Caesarean sections done in one hospital or in one man's practice which have what we at present regard as a low mortality, and this result is most likely to be obtained by unremitting care before, during and after operation, by approaching the individual problem with the thought that the last patient may have died, and the next one may die, but this one shall not, please God. Thus in 1957, L. G. Higgins recorded in *The Lancet* that in 14 years' personal practice of Caesarean section he had lost 2 mothers out of 1,114, one from the effects of eclampsia and one from pulmonary embolism. In Leeds Maternity Hospital, from 1950 to 1959 inclusive, 1,659 Caesarean sections (all but 14 through the lower segment) were performed by many different operators, with two deaths.

One of these two was a very obese woman with essential hypertension, admitted after 42½ weeks amenorrhoea with liquor coming away. Labour was slow on account of abnormal uterine action, and lower segment Caesarean section was carried out 52 hours after rupture of the membranes. She was pyrexial from the day of operation, and developed abdominal distension and vomiting. She was treated for ileus and died on the sixth day. General peritonitis was found post-mortem. There was healed mitral endocarditis, the valve barely admitting a finger, and the left ventricle was hypertrophied.

The other patient was a primigravida of 37 who was admitted as an emergency with moderate hypertension and meconium coming away. She had 43-weeks amenorrhoea, and the cervix was about 2-fingers dilated. Lower segment Caesarean section was done for foetal distress. Progress was satisfactory till the eighth day, when she had a sudden pulmonary embolus, and died within 1½ hours, the diagnosis being confirmed post-mortem.

The causes of death in both these cases are by no means unique.

A comment by Baird (1955) on Caesarean section bears repetition. He writes: "It is important to study a 'total' population to eliminate bias, otherwise percentages may be most misleading—for example, if they are derived from a hospital series only." When we pass from the individual series to the general mortality from Caesarean section for England and Wales as estimated by the Ministry of Health we are presented with a contrast, from mortalities of 1·8 (Higgins, 1957) and 1·2 (Leeds) per 1,000 on the one hand, to a minimum estimated mortality of 3·5 per 1,000 on the other. I may say that the Leeds series of sections for 1955 to 1957, the years on which the estimate of 3·5 per 1,000 was made by the Ministry, numbered 535, all through the lower segment, without a death. These figures are no rarity; as Baird (1957) has written: "In many maternity hospitals in Britain it is now by no means unusual to perform several hundred consecutive Caesarean sections without a death." Yet in the years under consideration there were reports on 184 deaths associated with section in England and Wales. Of these 4 were omitted from the detailed analysis, mainly on account of inadequacy of information. Of the remaining 180, 53 (29·4 per cent, or nearly a third) were considered to have an avoidable factor. The assessment of avoidability made by the Consultant advisers to the Ministry "reflects the most generally accepted standards of good antenatal and obstetric care" (1952–54 report). It may well be (as suggested in the 1955–57 report, p. 1) that the criteria for avoidability have become stricter in view of the generally higher standards of work, but my own measured opinion is that there is a slight tendency to err on the lenient side.

In contemplating critically deaths from Caesarean section, we may consider these points:

(1) The death may be that of a woman who would have died whatever the treatment, and the treatment by Caesarean section was correct, and skilfully carried out.

(2) The indication was wrong; the woman might well have survived if she had been treated otherwise.

(3) The technique was wrong: (*a*) Surgeon: the result might well have been better if someone else had done the operation; (*b*) Anaesthetist: the result might have been better if someone else had been responsible for the anaesthetic.

(4) The place of operation and the assistance available were unsuitable; had the patient undergone her operation in a well-staffed unit her chances would have been better.

(5) The decision to do Caesarean section was right, as it was calculated to reduce the risks to the patient, but it did in fact increase the risk of the particular complication of which the patient died.

(6) The decision to do Caesarean section was right, but it should have been made earlier.

Let us then take these points in more detail.

(1) *The Death may be that of a Woman who would have died whatever the Treatment, and the Treatment by Caesarean Section was Correct, and Skilfully Carried Out*

No doubt many of the deaths are in this category, and I do not propose to discuss them further.

(2) *The Indication was Wrong; the Woman might well have Survived if She had been Treated Otherwise*

Let us, as an example, consider heart disease. In the report on 1955–57 8 women who underwent Caesarean section on the indication of valvular disease or acute heart failure are said to have died of acute heart failure after it. It may appear remarkable that some patients were operated on with the indication of acute heart failure, but I have checked this point with the Ministry, and it is so (p. 33).

In other cases (p. 26) sections were performed on patients who had heart disease for other reasons. Seven such women died at the time of or immediately after the operation. One of them underwent it solely so that she might be sterilized, two for maternal and one for foetal distress, and one for breech presentation, although she had delivered herself without difficulty on five previous occasions.

It is surely best to consider heart disease as a contra-indication to section rather than as an indication. Hamilton (1959) in his chapter on Caesarean section in *British Obstetric Practice* states: "Heart disease in the absence of obstetric indications is not a reason for abdominal delivery." MacRae (1959), in his chapter on heart disease in pregnancy in the same work, writes: "There is a definite, though limited place, for Caesarean section in the patient with heart disease." He explains later that "There are occasions when Caesarean section is less of a risk to the patient" than vaginal delivery, and cites the simultaneous presence of obstetric abnormalities such as minor pelvic contraction and malpresentation. These may be responsible for prolonged labour with or without difficult delivery, and may cause fatal shock. But this group is a very small one, and in a series of 202 cardiac patients he had performed section only eight times. In the vast majority of patients section increases the dangers. Rest, carefully prescribed and carried out, frequent examinations to detect early signs of failure, and sometimes drugs, with the co-operation of a cardiologist, are the major needs during pregnancy: with suitable sedatives, and assisted delivery under pudendal block unless the second stage is progressing rapidly, during labour.

(3) *The Technique was Wrong*

(a) *Surgeon.* In some fatalities from section the basic error is in the technique used at the operation. It is therefore very much up to the consultants to see that their assistants are well instructed in this as in other techniques, and to see that they are not allowed to perform the operation unsupervised until they are efficient at it. Classical Caesarean section was perhaps the easiest abdominal operation; the lower segment operation is not quite so simple.

In discussing wrong technique I will instance the treatment of placenta praevia, and first mention one or two relevant points affecting the issue apart from the technique of the section. To obtain the best results in this condition it is first necessary to see that none of the patients attending the antenatal clinic is allowed to become seriously anaemic. The haemoglobin should be investigated at the first

visit and at the very least once more in the last two months. Iron should be given with no niggard hand, parenterally if time is becoming short. Transfusion should be carried out if the haemoglobin is still low in the last month. "In only 39 of the 138 deaths from ante- and post-partum haemorrhage was there a record of even one haemoglobin estimation" (1955–57 report).

Twenty-eight of the fatalities reported on in the same Ministry report were from placenta praevia, and avoidable factors were present in 12. There were at least 10 patients who died from loss of blood when Caesarean section had been done for the condition: in all of these the operation notes stated that large blood vessels were seen on the lower segment. The standard transverse incision was made in all cases and this was followed by severe haemorrhage.

Thanks to the writings of Macafee, Marshall, and Moir, among others, it is well recognized that the lower segment operation is almost always the appropriate one for placenta praevia. But the chance of abnormal bleeding occurring during the operation should always be taken into account. A simple but valuable measure is to set up a blood transfusion, if possible some time before the patient is anaesthetized, so that any reaction may be observed before the start of the operation. Then if blood-loss is unexpectedly heavy, the rate of the transfusion can readily be increased.

The operation should not be started with the *idée fixe* that it is to be done through the lower segment, come what may. It is a mistake to become clamped in the vice of an absolute rule. Macafee (1960), no advocate of the classical operation, points out the difficulties of the more modern technique if there is a poorly developed lower segment or if that area is obliterated by adhesions. In such cases there is a place for the classical operation, but it will seldom be needed. If the lower segment is particularly vascular, this is generally an indication "for rapid enlargement of the incision" in it "with rapid but careful extraction of the baby". It may be possible to push the placenta to one side, after making a small stab wound with a scalpel. If there is bleeding which cannot be controlled, the decision to do hysterectomy must be taken without delay.

In the rare instances when the patient's general condition has deteriorated while she is still at home, the Flying Squad should be summoned to resuscitate her before she is moved to hospital.

(b) *Anaesthetist.* Forty-nine deaths occurred in 1952–54 from complications of anaesthesia, besides a further 20 at least in which anaesthesia was a contributory factor. Among the 49, 13 or just over one-quarter were associated with Caesarean section. In 1955–57 anaesthetic deaths numbered 31, and 10 of these are stated to have been due to inhalation of stomach contents during section.

The importance of tracheal intubation, of having suction apparatus available and of emptying the stomach before the anaesthetic is given, is mentioned in both the reports. Caesarean section is a special problem for the anaesthetist, and deaths from inhalation of gastric contents are more liable to occur when the patient has been in labour for a considerable time. An anaesthetist experienced in obstetric work should be available whenever possible.

Local anaesthesia reduces the risks just mentioned.

(4) *The Place of Operation and the Assistance Available were Unsuitable*

In order that necessary surgical procedures such as Caesarean section may be carried out with maximum efficiency, it is a great advantage to a maternity unit that it should be part of a general hospital, or associated with a gynaecological department. The staff in a purely maternity unit may often be in the following position. It cannot attract or maintain an experienced theatre nursing staff, because the surgical operations done are limited in numbers and in variety. Nursing staff who undertake the assisting, therefore, through no fault of their own, do it as an occasional task and often do not develop that use which is second nature. Sometimes the house surgeon is doing a pre-registration appointment and has not previously done six months surgery, so that he is unaccustomed to assisting at laparotomy. People with only intermittent and infrequent experience are much less likely to be perfect in their aseptic technique than those who are constantly playing their parts in an operating team. It may be

difficult or even impossible to obtain an experienced anaesthetist at short notice.

When an obstetric unit is associated with gynaecological beds or is part of a general hospital, it is vital, if babies' and sometimes even mothers' lives are not to be lost, that there should be immediate access to a theatre. It still happens that sometimes an urgent Caesarean section has to wait its turn in a list of surgical acute cases. A complete laparotomy set should always be held ready sterilized, to minimize delay.

If the patient is in a private nursing home she may be even worse off than in a maternity hospital. A nursing home that accepts surgical patients may well be not very experienced in dealing with sections. Another situation that sometimes arises may be worse still for the patient. She is in a maternity nursing home with no operating theatre; Caesarean section becomes indicated; the nursing home does not wish to part with the patient. Pressure is put on the obstetrician to operate in unsuitable surroundings, with an improvised theatre and inexperienced helpers. If he is not strong-minded he will yield, and so considerably increase the risk to his patient.

(5) *The Decision to do Caesarean Section was Right, as it was Calculated to Reduce the Risks to the Patient, but it did in fact Increase the Risk of the Complication from which the Patient Died*

The deaths from section considered in the Ministry's report for 1952–54 included 32 from pulmonary embolism, or 18·3 per cent of the total. In the second series, 1955–57, there were 33 deaths from pulmonary embolism, again 18·3 per cent, but in 7 of these the embolus was regarded as a terminal event. Embolism was fourth commonest of the causes of maternal death in 1952–54, but in 1955–57 had risen to second place. Avoidable factors were not often considered to be present (from 1952–54 in 10 per cent, from 1955–57 in 6·5 per cent) and they were related mainly to the way predisposing conditions such as bleeding or anaemia were managed, rather than to the management of pulmonary embolism itself. The authors of the report obviously take the view that in the light of our present knowledge it is not reasonable to regard embolism as a preventable cause of death. It is a question how much longer we shall be justified in holding this belief. Pulmonary embolism has exercised the minds of surgeons in all branches of surgery for many years, and steps have been taken with a view to reducing its incidence. These have included improved positioning on the operating table, as advocated by McNeill Love, and early ambulation, which has become widespread. In spite of these measures, the condition looms large as a cause of death after Caesarean section.

Chalmers, Marks, Bottomley and Lloyd (1960) have recently reported results of a 5-year study on their obstetric and gynaecological patients in which routine prophylactic anticoagulants were used. It is widely held that such patients have a special liability to thrombosis and embolism. Because of limited numbers of pathological staff, the authors selected certain classes of case most prone to embolism for the prophylaxis. These included (1) major operations in patients over 40, (2) operations for gynaecological malignancies at any age, (3) major operations at any age on women with a history of thrombophlebitis, and (4) all Caesarean sections. The total number of patients treated (1,877) included 317 who underwent Caesarean section.

The first dose of phenindione (Dindevan, Evans) was given on the 3rd day after operation, and varied between 50 and 200 mg. according to the patient's age. A daily dose was given to keep the prothrombin concentration at 15 to 30 per cent until the tenth day at least, and longer if the patient was still being kept in bed. A comparison was made between the five years during which the trial was held (1954–58) and the previous 7 years (1947–53). Non-fatal embolism was reduced from an average of 4·2 in these years to 1·2 in the study years, and fatal embolism from 1·8 to 0·4. "The number of admissions, the types of case relative to disease, age and operation, and the post-operative care did not appreciably alter except as regards the use of anticoagulant over the whole twelve years." The authors conclude that the results justify adoption of the method as a routine for

the types of operation specified in view of the known high incidence of thrombo-embolism after them. This approach holds out a hope for the prevention of thrombosis and embolism.

The Ministry estimates in the recent report that 3·8 per cent of deliveries in National Health Service hospitals are by section; this leaves 96·2 per cent for vaginal deliveries. The number of vaginal deliveries is thus 96·2/3·8 or 25·3 times as great as the number of sections. The number of fatal pulmonary emboli after section is 26 at the lowest estimate, after vaginal delivery 114, or 4·4 times as many.

The risk of fatal pulmonary embolism may therefore be taken as 25·3/4·4 or nearly six (5·75) times as great as after vaginal delivery.

(6) *The Decision to do Caesarean Section was Right, but it Should have been Made Earlier*

It has been known for many years (Amand Routh, 1911; Kerr and Holland, 1921; Marshall, 1939) that the later in labour it is done, and especially the longer after rupture of the membranes, the greater the risk of section.

Every now and then a patient is sent into hospital late in labour, obstructed, so that the hospital staff has no opportunity of dealing with her at the optimum stage, before or at least early in labour. The patient herself may have been at fault in not seeking antenatal care, those providing antenatal care may have been unobservant or careless, those in attendance at labour may have shown similar faults. At the time when the patient is first seen in hospital the least dangerous line of treatment may still be Caesarean section, but it would have been a good deal safer had it been carried out earlier.

There are also booked patients who are watched for too long in hospital, and then operated on when the risk has become greater. There is always this dilemma; if the decision to operate is made early it is likely that many unnecessary operations will be done, while if there is delay the danger of the operation increases. Baird (1955) has pointed out that if the first course is adopted the case mortality is likely to be low but just as many women may die because of the much larger total of operations.

The recent Ministry report states that in at least 13 of the fatal cases obstructed labour was treated by section, with one or more avoidable factors present. Ten of the 13 were "failed forceps" cases; I do not propose to go now into the reasons why the obstetrician should not embark on a forceps operation without a justifiable hope of being able to complete it. The report comments on the unwisdom of leaving decisions on these difficult cases to residents of no great experience. In regard to this there are two points to make. First, the decision whether section or some other treatment is the right one may call for mature judgment. Secondly, the operation may be specially difficult when the head is wedged in the pelvis. The Wrigley forceps is often useful in achieving controlled extraction. It has also been suggested that the head may be disimpacted most readily by means of a hand passed behind the uterus before it is opened.

A remark which I heard made many times by a distinguished surgeon when I was a medical student and a young doctor thirty years and more ago was this: "Surgery has reached the limit of its possible achievements." What an unwise remark this was, and how it has been falsified; consider for instance the advances in thoracic and in neurosurgery in the last thirty years. There is a tendency for obstetricians in these days to say or write some such remark as "The problem of maternal mortality would appear to have been solved during the last 25 years". Far be it from me to underestimate the achievements which have led to the colossal drop in maternal mortality over this period. But we know that, with two notable exceptions, to which I have already made allusion twice in the southern capital earlier this year, these achievements have been made by non-obstetricians, and have improved mortality over the whole field of medicine. There are still improvements which the general body of obstetricians can make. The Ministry report for 1955–57 which I have cited so often estimates that in over 40 per cent of the maternal deaths there were avoidable factors. Unquestionably one of the things still capable of improvement is the mortality from Caesarean section, as there were avoidable factors in 53 cases (29·4 per cent); and it may well be that we shall find in

the next few years that for some conditions for which it is now used it will become out of date. I cannot for instance believe that section will always be the last word in the management of abnormal uterine action. Surely a drug regulating the action of the uterine muscle will be discovered one day that will make surgery for the condition unnecessary.

Thanks to the kindness of Sir Eardley Holland, a great friend and co-writer on Caesarean section in the past with Munro Kerr, I am able to quote the last lines of a foreword he has written to a book by Dr. P. Schwartz, an American pathologist, unpublished but in the press. He puts rather a different point of view from the one I have been presenting to you:

"Only a morbid anatomist and pathologist of Dr. Schwartz's eminence would have the delightful and logical temerity to write: 'It is best to be born at term by cesarean section before the onset of labour.' But why not? It is already being done sporadically. Modern cesarean section with local analgesia has a maternal mortality no greater than that of natural childbirth with its unforeseen complications and, there being no birth injury, the perinatal mortality is much less. And cesarean birth would be a sort of millennium for women: no more relaxed vaginal outlets and utero-vaginal prolapse, goodbye to torn and infected cervices and cancer of the cervix. And surgical technique marches on and on. So, one day, why not? But my 'natural childbirth' conscience pricks me nevertheless."

Some of you may be more in sympathy with these opinions.

As my last word I should like to assure you, in case any of you are doubting it, of my awareness that our object in all these matters is to obtain the minimum mortality and morbidity to mother and child, not to do the minimum number of Caesarean sections.

I should like to acknowledge the help I have received from Dr. Roma Chamberlain of the Ministry of Health in the elucidation of some of the statistics, to the authors of the two Ministry reports for facts on which to base my address, and to my colleagues at Leeds for access to their case reports.

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THE DEPENDENCE OF UTERINE MUSCLE CONTRACTION ON pH, WITH REFERENCE TO PROLONGED LABOUR

BY

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INTRODUCTION

AMONG the causes of prolonged labour, disorders of uterine action are the most common and remain the least understood (Sturrock and Brown, 1956; Keettel and Pettis, 1956; Fields *et al.*, 1959).

One variety, usually known as hypotonic uterine inertia, seems more amenable to analysis than others because uterine contractions are apparently normal in type, the defect being in their low frequency of occurrence and the diminished force of each contraction. It is as if something is depressing the excitability and contractile efficiency of the uterine muscle while, in contrast to other types of disorder, the organization of cycles of contraction and relaxation is unimpaired. The nature of this presumed myometrial depressant has interested a number of investigators and some important contributions to its possible nature have been made.

Kaiser and Harris (1950) found that intravenous infusion of low concentrations of adrenaline inhibited uterine contractions of women in normal labour and surmised from this that emotional stress might excite secretion of sufficient endogenous adrenaline to depress uterine action. Following on from this Garciá and Garciá (1955) showed a correlation between long and painful labours and the ability of samples of blood plasma to inhibit carbachol-induced contractions of rat uterus. Adrenaline-like substances were held responsible for this blocking action *in vitro* as for the ineffective uterine action *in vivo*.

A study of blood electrolytes during labour by Hawkins and Nixon (1957) revealed that after 48 hours there was a considerable fall in potassium level, which in conjunction with changes in sodium and chloride was felt to be due to adrenal cortex hypersecretion. They offered the hypothesis that hypopotassaemia might play a part in depressing myometrial function and further prolonging labour.

Cort and Cort (1957) showed by direct analysis of uterine electrolytes that there is normally a fall in the concentration of intracellular potassium in the third trimester of pregnancy and a further fall in labour. Prolonged and ineffective labours were found to be associated with potassium levels which were slightly, though significantly, lower than in normal cases and these authors also suggested that potassium deficiency might have been responsible for the poor quality of uterine contractions. Blood electrolytes were estimated as part of this study and among other changes reported was the fact that during labour the majority of patients developed some degree of metabolic acidosis. This was considered by Cort and Cort as a factor in the loss of cell potassium but it also raises the question of whether the inhibition of uterine contractions in inertia might be due to a direct effect of hydrogen ions on uterine muscle rather than to the slight diminution of intracellular potassium levels. Indeed Hawkins and Nixon (1958) have already pointed out that loss of intracellular potassium *per se* need not necessarily prolong the course of labour.

The maintenance of acid-base balance in the body depends to a large extent on the capacity of the blood to carry acid end-products of

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metabolism with minimal change in pH. As far as non-volatile acids are concerned a most important buffer is the bicarbonate-carbonic acid system. Addition of acid tends to convert bicarbonate to carbon dioxide which is excreted through the lungs so that the ratio of bicarbonate to carbonic acid, on which pH depends, is kept constant. The lowered bicarbonate concentration can be restored to normal when the acid radicals are either metabolized or excreted in the urine; the rate of respiration being adjusted to allow a proportional build-up of carbon dioxide so that the bicarbonate-carbonic acid ratio again does not alter.

It is well known that blood from pregnant women has a lower bicarbonate content than is usually found in the non-pregnant state. This reduction in alkali reserve does not alter pH because there is also an increase in pulmonary ventilation which lowers blood carbon dioxide tension (Hasselbalch and Lundsgaard, 1912; Marrack and Boone, 1923; Oard and Peters, 1929; Boutourline-Young and Boutourline-Young, 1956). During pregnancy the buffering capacity of a sample of blood is less than usual although, in terms of the resistance of the whole body to pH change, this may not necessarily be very significant as the increase in blood volume may compensate for the reduced concentration of the components of the bicarbonate buffer. Whatever the state of the body buffers in pregnancy it has been shown that during labour there is an increase in the production of endogenous acid. This has been demonstrated by Hendricks (1957) and Gemzell *et al.* (1957) who found an increase in blood lactic acid levels and also those cases who show ketonuria, a moderately common finding in labour, presumably have acid ketone bodies circulating in the bloodstream. In addition to the extra load that these metabolites place on buffering mechanisms there is the possibility that excretion of acid may be impaired by the reduction in the rate of urine secretion which is often seen even in normal labours (Theobald, 1959).

Apparently in the great majority of cases these factors do not interfere with childbirth but the changes are such that one would expect the degree of disturbance in acid-base state to become greater the longer labour progressed. It was therefore thought that if labour went on for an unusually long time the decline of uterine contractility in secondary uterine inertia could possibly be due to depression of the myometrium by mounting tissue acidity. This line of approach was encouraged by an examination of the case records of a small series of primigravidae who had undergone Caesarean section for prolonged labour. In the last three years at the National Women's Hospital, 6 out of the 6 cases of true secondary uterine inertia had ketonuria during the 24 hours before operation whereas ketonuria was found in only 3 of the 11 cases who showed normal uterine contractions to the end.

The experiments reported below were designed as a partial test of the hypothesis that a shift of acid-base balance towards the acid side may contribute to secondary uterine inertia. They describe the effects of hydrogen ion concentration on the spontaneous contractility and oxytocin sensitivity of excised strips of pregnant human uterine muscle.

Methods

All experiments were done on muscle obtained from pregnant human uteri, opened at Caesarean section in the last one or two weeks of pregnancy. In one case a piece of upper segment was excised but in all others a slice of muscle was cut transversely from the upper margin of the lower segment incision. The patients were premedicated with hyoscine hydrobromide 1/150 gr. and the operation was carried out either under epidural anaesthesia or under thiopentone, nitrous oxide and d-tubocurarine chloride. The muscle strip was removed before the injection of ergometrine or oxytocin, placed in a covered Petri dish moistened with a little normal saline and put in a refrigerator. Serial experiments done on samples from one piece of muscle stored this way showed that spontaneous motility was retained undiminished for at least 67 hours, but all experiments reported below were done on muscle which had been kept not longer than 48 hours. Experiments were done on 25 strips of which two were discarded as unsatisfactory because of highly irregular spontaneous contractions. In almost all cases only

one muscle strip was taken from each patient. Several strips which showed no spontaneous motility at all are not included in this total.

For recording contractions a slice of muscle about 20 mm. long and 3 mm. thick was suspended between two platinum wire loops in a glass tube of 15 ml. capacity. The lower platinum loop was fixed to a cork in the bottom of the tube and the upper was attached by a straightened platinum wire to a strain gauge. The glass tube and the strain gauge above were both held in cast aluminium clamps fixed to a heavy steel upright arising from a steel base-plate. The apparatus was extremely rigid and a fine screw on the head holding the strain gauge permitted accurate adjustment of the resting tension of the muscle strip.

Two plastic tubes passed through the cork in the bottom of the muscle tube, one leading from the gas cylinders containing oxygen and carbon dioxide mixtures and one from the reservoir bottles of solution. Solutions were moved from the various reservoir bottles to the muscle bath by means of a system of plastic tubes and 3-ways taps attached to a 50 ml. syringe. As fresh solution was run into the lower end of the muscle bath the overflow was removed at the top through a side arm connected to a vacuum line.

Reservoir bottles, syringes, plastic tubes and the muscle bath were all immersed in a water bath held at 37 degrees Centigrade in order that changes of solution could be made with no change of temperature. The solutions in the reservoir bottles as well as the solution in the muscle bath were kept gassed by the appropriate oxygen and carbon dioxide mixtures.

Muscle tension was recorded by means of a Statham temperature compensated unbonded strain gauge. The strain sensitive elements are arranged in the form of a Wheatstone bridge which in this case was powered by 6 volts (R.M.S. value) from a sinusoidal oscillator of frequency 2 Kc/s. An external balancing circuit was provided. Signals were amplified by a three-stage amplifier, the rectified output of which was led to an Evershed and Vignoles recording milliammeter. This equipment responded linearly to tensions between 200 mg. and 50 g. with a change of muscle length of less than 0·02 mm.

Ringer Tyrode (*British Pharmacopoeia*, 1934) formed the basis for solutions used. This contains 136·8 mMol. of sodium chloride and 11·9 mMol. of sodium bicarbonate per litre. In addition two variants were made up containing 23·8 and 35·0 mMol./L of $NaHCO_3$ respectively. The higher concentrations of $NaHCO_3$ were osmotically compensated by an appropriate reduction in the concentration of NaCl.

Solutions were gassed by oxygen and carbon dioxide mixtures in which CO_2 concentration, measured by a Liston-Becker infra-red CO_2 analyzer, varied between 2 and 10 per cent.

pH was measured with a glass electrode, pH measuring unit and Vibron Electrometer manufactured by Electronic Instruments Ltd. (Surrey, England). The pH measuring chamber was of the type described by Wynn and Ludbrook (1957) in which the pH of small quantities of fluid may be measured anaerobically at a constant temperature. Samples of solutions were gassed in the pH measuring chamber for several minutes using the same gas mixtures as had been used in the experiments and the pH measured without further contact with the air. Measurements were made to two places of decimals and are quoted below rounded off to the nearest 0·05 of a pH unit.

Results

After the muscle strips had been set up in the organ bath and attached to the strain gauge they remained quiescent for a variable time, in some cases as long as three hours. During this period the resting length was adjusted as described by Csapó (1954). The muscle was slowly stretched, by means of the screw on the strain gauge bracket, until it reached the greatest length to which it would adapt with no sustained increase in resting tension. Motility first showed as low amplitude waves which built up over the next few hours to higher amplitude contractions of fairly regular frequency. No experiments were done until this steady state was reached. In this series there was no characteristic feature of the steady state contraction pattern of different strips which could be correlated with either the length of pregnancy or with any pathological condition

which may have led to the Caesarean section being performed.

(1) *The Effect of pH on Spontaneous Motility*

When a baseline of activity had been established as described above the bath was washed out several times with the same solution. This was done at intervals and the record of contractions observed to make sure that mere replacement of solution without changing its composition did not alter the motility pattern. Following this the pH of the bathing solution was changed either by substituting solutions of varying sodium bicarbonate content or by gassing with different mixtures of oxygen and carbon dioxide and any effect on muscle contraction observed.

Figure 1 shows the spontaneous motility of a piece of muscle in two solutions the pH values of which depended in this case on their respective $NaHCO_3$ contents. CO_2 tension was kept constant throughout while the solution in the bath was alternated between one containing 35·0 mMol. of $NaHCO_3$/L. and one containing 11·9 mMol. $NaHCO_3$/L. It can be seen that the strong contractions occurring at pH 7·65 were abolished by reducing the pH to 7·20 and reappeared when the muscle was again bathed in the more alkaline solution.

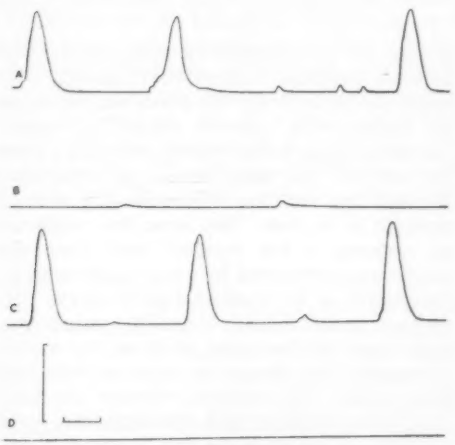

FIG. 1

Tracings of spontaneous contractions of a strip of uterine muscle. Isometric recording. Carbon dioxide tension was kept constant by bubbling a mixture of oxygen 96 per cent and carbon dioxide 4 per cent through the bath.
A and C: Bicarbonate concentration in solution 35·0 mMol./L. pH 7·65.
B and D: Bicarbonate concentration in solution 11·9 mMol./L. pH 7·20.
The records were made in the order A, B, C, D.
Calibration marks: vertical 20 g., horizontal 2 minutes.

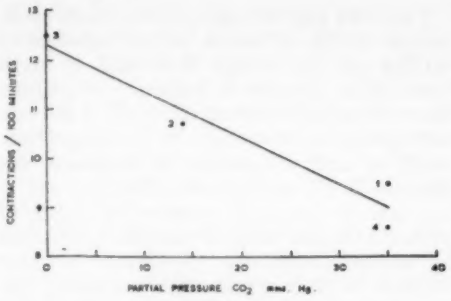

FIG. 2

A graph showing the relationship between the frequency of spontaneous contraction of a strip of uterine muscle and the partial pressure of carbon dioxide bubbling through the bathing fluid. The bicarbonate concentration was kept constant at 11·9 mMol./L.
Numbers beside the points on the graph show the order in which records were made.
pH value at points 1 and 4, 7·10; at point 2, 7·55 and at point 3, 8·45.
The regression line of rate of contraction on CO_2 partial pressure shows P between 0·05 and 0·02 (t test).
Note the suppressed origin on the vertical axis.

The effect of a change in pH brought about by changing the CO_2 tension in the bathing fluid is shown in Figure 2. This piece of muscle showed excellent stability as far as its motility pattern was concerned and it was possible to record contractions over a long period (4 hours 8 minutes for the results illustrated) and make reliable measurements of average frequency. The $NaHCO_3$ content was constant at 11·9 mMol./L. As the graph shows, reducing CO_2 tension from 35 to 14 mm. of mercury and then to zero increased the average rate of contraction. When the CO_2 tension was restored to 35 mm. of mercury the frequency of contraction fell to approximately the original level. The pH changes were from 7·10 to 7·55 to 8·45 and back to 7·10.

Collecting together observations on the spontaneous motility of muscle strips in solutions of varying pH, 25 changes from acid to alkali produced an increase in frequency of contraction in 18 and an equivocal effect in 7. A decrease in frequency was never seen. In 20 changes from alkali to acid a decrease in frequency was observed in 17, an equivocal effect in 2 and in one case the frequency increased. A change of pH had a variable effect on the tension developed by muscle contraction. Sometimes a more alkaline solution would slightly enhance the strength of contraction but at other times, when an increase in rate was marked, maximum tension would decline a little.

(2) *The Effect of pH on Oxytocin Sensitivity*

There is evidence to indicate that secretion of oxytocin by the neurohypophysis is an important factor underlying uterine contractions in normal human labour (Theobald *et al.*, 1956; Caldeyro-Barcia and Poseiro, 1959). It was therefore important to investigate *in vitro* the effect of hydrogen ion concentration on oxytocin induced muscle contractions.

In many cases the frequency of spontaneous contraction of muscle strips declined towards the end of the day and experiments on oxytocin sensitivity could be carried out without interference. When this decline in frequency did not occur spontaneous activity could be all but abolished by lowering the temperature of the water bath to between 30 and 32 degrees centigrade. Muscle from the lower uterine segment is particularly suitable for this type of experiment as it tends to show less spontaneous motility than muscle strips cut from the body or fundus (Sandberg *et al.*, 1958).

Syntocinon (Sandoz) was used, diluted with normal saline until 1 ml. contained 0·01 of a unit of oxytocin. The solution was drawn up in a tuberculin syringe and a suitable dose, always less than 1 ml. of the diluted solution, was injected into the bath. Before each fresh dose of oxytocin the bath was washed out with at least three times its volume of the appropriate solution.

Tracings in Figure 3 illustrate the inhibitory effect of increased acidity on the oxytocin response of a uterine muscle strip. In the upper tracing pH was changed by using solutions of different $NaHCO_3$ content (CO_2 content constant) and in the lower the effect was produced by altering CO_2 tension ($NaHCO_3$ content constant). It can be seen that in both cases when the medium was more alkaline a contraction followed the addition of 0·003 of a unit of oxytocin to the bath. This same dose produced no response a few minutes later when the muscle was surrounded by a more acid medium, irrespective of the method used to lower pH. As soon as the solution round the muscle was made more alkaline again, however, the muscle contracted even though no extra oxytocin had been added. This occurred whether the bath solution was replaced with one containing more $NaHCO_3$ or whether the CO_2 content of gas bubbling through the bath was lowered. Further oxytocin injected into the now alkaline medium resulted in another contraction.

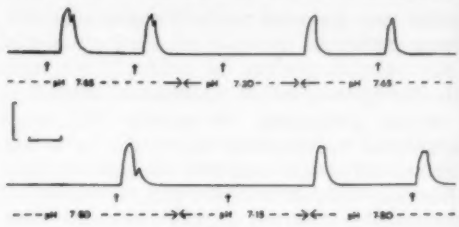

FIG. 3

Tracings of isometrically recorded contractions of a strip of uterine muscle. At each arrow 0·003 of a unit of oxytocin (Syntocinon, Sandoz) was added to the bath. In the top tracing pH was changed by varying the bicarbonate concentration while the carbon dioxide tension was kept constant, and in the bottom tracing bicarbonate concentration was constant and carbon dioxide tension altered. The bath was washed out with the appropriate solution before each new dose of oxytocin. Note that, in both upper and lower tracings, there is no response to oxytocin in the more acid solution but a contraction appears, without further oxytocin, when the solution round the muscle strip is made more alkaline. Calibration marks: vertical 20 g., horizontal 2 minutes.

It is an interesting finding that the oxytocin added to a relatively acid medium may cause no contraction until the bath has been washed out and filled with a more alkaline solution. Presumably the oxytocin becomes fixed to the muscle but for some reason is prevented from

exciting a contraction until the hydrogen ion concentration in the environment falls. Mechanical or thermal stimulation occurring as the solution was changed is an unlikely explanation. Precautions were taken to ensure that these changes could be made with no alteration of temperature or disturbance of fluid level in the bath and, besides, the same results were seen when the pH change was made by lowering the CO_2 tension.

A slightly larger dose of oxytocin could usually be found which would produce a large contraction in an alkaline solution and a small one in acid. In the pH range investigated, 7·15 to 7·80, increasing the dose of oxytocin would counteract the depressing effect of increased acidity.

Since studies of labour induced by an intravenous oxytocin drip have suggested that regular uterine contractions in normal spontaneous labour are probably a response to the continuous secretion of oxytocin by the neurohypophysis an attempt was made to reproduce similar conditions in the laboratory by setting up a constant rate drip apparatus and slowly infusing a dilute Syntocinon solution into the muscle bath. The drip rate was recorded electronically and displayed on the paper recording muscle contractions so that a check of rates of infusion could be kept. The oxytocin solution was led to the bottom of the bath by a fine plastic tube and the fluid level kept constant by a vacuum line connected to the side arm at the top. Bubbles of gas passing through provided sufficient agitation. For this purpose the oxytocin was diluted with the same solution as used in the muscle bath. It proved impracticable to alter pH by changing bathing solutions so observations were restricted to the effect of different CO_2 tensions.

Figure 4 shows the results of one of these experiments. Oxytocin was infused at a constant rate throughout but, as the illustration shows, the resulting frequency of muscle contraction could be modified by altering the percentage of CO_2 in the gas bubbling through the bath. Once again low CO_2 tension (high pH) was associated with a higher rate of contraction and high CO_2 tension (low pH) reduced the frequency.

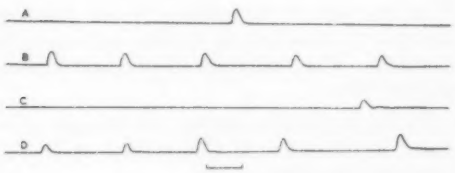

FIG. 4

Tracings of isometric contractions of a strip of uterine muscle recorded in response to a continuous oxytocin drip.

The bicarbonate concentration was constant while the pH was changed by varying the mixture of oxygen and carbon dioxide bubbling through the bath.

A and C: Carbon dioxide 10 per cent. pH 7·15.

B and D: Carbon dioxide 2 per cent. pH 7·80.

Records were made in the order A, B, C, D.

Calibration mark: 2 minutes.

DISCUSSION

This investigation has shown that contraction of human myometrial strips excised in late pregnancy is in part dependent on the pH of the medium bathing the muscle. All but one of the experiments were done on samples from the lower segment but as similar results were seen in the one experiment on upper segment muscle the findings probably apply to the whole of the myometrium at this stage of pregnancy. It seems apparent that changes of pH did determine the results although it has not been established whether carbon dioxide or bicarbonate have additional actions of their own. In view of work on other tissues (arterial muscle, Tobian *et al.*, 1959; heart muscle, Williams, 1955) they probably do, but the fact that similar effects were produced in the present experiments by pH changes due to alteration of either CO_2 tension or HCO_3^- concentration alone, seems adequate evidence that hydrogen ion concentration is a critical factor. Halpern *et al.* (1959) have done some experiments on oxytocin sensitivity of guinea-pig uterine muscle bathed in bicarbonate buffers of varying composition and have obtained similar results. On the basis of pH changes in maleate buffers however they decided that carbonic acid itself and not hydrogen ion concentration was responsible for the changes in sensitivity they observed.

Nevertheless it is felt that although CO_2 may produce a greater effect, probably because of its solubility in cell membranes (Caldwell, 1958), it is not possible to exclude an action due to changes in pH. The fact remains that in experiments on pregnant human uterine muscle both an inhibition of the rate of spontaneous contraction and a reduction in oxytocin sensitivity have been demonstrated when the pH of the bathing solution was reduced by lowering HCO_3^- concentration, the sort of disturbance found in a metabolic acidosis.

The literature on the effects of CO_2 and pH on biological systems is voluminous and often contradictory. In the case of uterine muscle Evans and Underhill (1923) showed that when the pH of the medium bathing guinea-pig uterus was above 5 or 6 the addition of acid would result in contraction. Bentley and Dicker (1955) found a similar type of effect when assaying oxytocic activity and emphasized the importance of control of pH in this procedure, a point well supported by the present work. On the other hand Hemingway (1926) found that a brief increase of environmental pH would increase the sensitivity of cat uterus to posterior pituitary extract. Some experiments done in this laboratory (Mark, unpublished) on guinea-pig uterus have suggested that contradictory effects might depend on the hormonal state of the uterus rather than on a species difference and also that different results may follow uterine contractions occurring spontaneously or as a response to oxytocin.

The mechanism of the pH effect on pregnant human uterine muscle remains quite unknown. A careful study of the action of pH, CO_2 and HCO_3^- on excised rabbit auricles (Williams, 1955) indicates that the underlying factors are liable to be complicated and that separate analyses of membrane phenomena, contractile mechanisms and energy metabolism in muscle must be undertaken and that secondary effects on calcium and potassium ions in particular must be determined before a clear account can be given. When a drug effect is analyzed in relation to pH changes the question of ionization at different pH values must also be considered.

As for the problem of secondary uterine inertia it has been shown that variations in pH, not much greater than those found in arterial blood, have *in vitro* a well marked effect on pregnant human uterine muscle. In the body, however, cells are generally bathed in tissue fluid, the composition of which is probably more nearly reflected by the venous blood draining the organ than by the arterial blood supplying it. In the absence of a more direct index of extracellular pH it is possible that careful estimation of the acid-base state of arterial blood correlated with a record of uterine contractions might give an indication of whether or not myometrial function in labour is liable to be endangered by falling pH. If, as is likely, labour contractions produce acid metabolites, a reduction in buffering power of the blood even with minimal change in arterial pH, coupled with the reduction in uterine blood flow that has been shown to occur in some labours (Wright *et al.*, 1958), may allow a rapid increase in tissue acidity with each contraction. The dependence of contraction on pH in isolated muscle strips is such that it is possible that this could be sufficient to diminish uterine contractions to the point of inertia. Nevertheless it is felt, in agreement with Hawkins and Nixon (1957), that careful attention to calorie intake and fluid and electrolyte balance during a protracted labour may do much to prevent the occurrence of secondary uterine inertia.

Summary

(1) The pH of the bathing Tyrode solution modifies the spontaneous motility and oxytocin sensitivity of excised strips of pregnant human myometrium.

(2) Similar effects follow pH changes produced by alteration of CO_2 tension or HCO_3^- concentration alone.

(3) In the pH range 7·1 to 7·8 the rate of spontaneous contraction is increased by alkali and decreased by acid.

(4) Within the same range oxytocin sensitivity is enhanced by alkali and reduced by acid.

(5) The possible significance of these findings in relation to the clinical problem of secondary uterine inertia is discussed.

Acknowledgments

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THE DIFFERENT LIGAMENTS OF THE SYMPHYSIS PUBIS IN THE PREGNANT AND THE NON-PREGNANT STATE

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REVIEW OF LITERATURE

THE Hippocratic theory of "disjunctio pelvica" was debated by Vesalius (1543), Hunter (1762), Cantin (1899), Lushka (1912) and many others. Their views differed widely. Some believed that relaxation of the pelvic joints was a constant phenomenon and others that it was only an uncommon pathological one. Hippocrates held that the pelvis separated at the time of the first labour and did not unite again thereafter. Vesalius (1543) advanced the concept that the pelvis is a comparatively unyielding bony ring. Duncan (1868) noted separation of the pelvis in the cow at term. Increased mobility in the joints of 490 out of 500 pelves during pregnancy was found by Cantin (1899), whereas Reis, Baer, Arens and Stewart (1932) were unable to demonstrate any change in the pelvic articulations of 80 consecutive cases. They concluded that any increase in the span of the pelvis takes place only during labour. On the other hand, Roberts (1934) stated that additional separation of the pelvic bones in labour is very slight and is observed only in few cases.

The clinical significance of the separation of the symphysis pubis in the human has been regarded as of serious import. De Lee (1943) looked upon the complication as so serious that it entailed a mortality of about 35 per cent. James (1944) states: "Rupture of the pelvic girdle during labour is a serious accident which carries with it a high mortality."

Our interest in the subject was aroused by the fact that we met three cases of rupture of the symphysis pubis in one year, although we had not met a single other case in the course of the previous ten years. Also one of us (A.I.) has had practical experience with symphysiotomy when it was in vogue.

In a previous work we (Ibrahim and El-Sherbini, 1960) considered the effect of parity as well as of pregnancy during the last three months on the interpubic space.

In the present work the authors discuss the cases of rupture of the symphysis encountered by them, as well as a study of the changes in the different ligaments of the symphysis pubis as affected by sex, parity and advanced pregnancy. The histological and histochemical changes in the structures of the symphysis pubis are now being studied and will be published later.

ANATOMY

The symphysis pubis is a secondary cartilaginous joint. The symphysis is coated with hyaline cartilage which is united to its fellow on the opposite side by an intervening disc of fibrocartilage. A small cavity in the form of a vertical slit, not lined by synovial membrane, can be demonstrated in the upper and back part of this disc. It only appears after the eighth to the tenth year of life and is probably formed by softening and absorption of the fibrocartilage.

There are four ligaments; the anterior, the posterior, the superior and the inferior. The anterior ligament is of considerable thickness and is made of an interlaced decussation of fibres. It is strengthened by the medial tendons of origin of the two recti muscles as well as by the fibres of the external oblique aponeuroses. The inferior, arcuate or subpubic ligament is also of considerable thickness. It forms part of the boundary of the inferior aperture of the pelvis. The superior ligament is much thinner and consists of transverse fibres passing between the two pubic crests. The posterior ligament is very thin and is formed of relatively few fibres running transversely.

The Pubic Symphysiometer
(Fig. 1)

To study the strength of the different ligaments of the symphysis pubis we devised a special apparatus to which we gave the name "Pubic

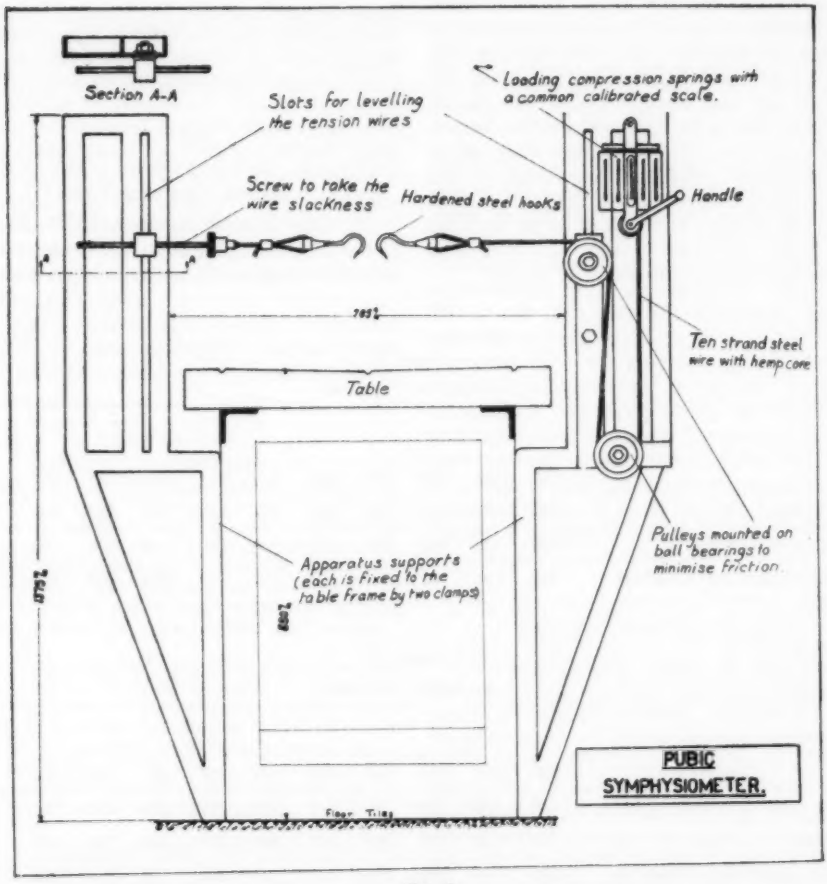
Section A-A
Slots for levelling the tension wires
Loading compression springs with a common calibrated scale.
Screw to take the wire slackness
Hardened steel hooks
Handle
Ten strand steel wire with hemp core
Table
Pulleys mounted on ball bearings to minimise friction.
Apparatus supports (each is fixed to the table frame by two clamps)
Floor Tube
PUBIC SYMPHYSIOMETER.

Fig. 1

Symphysiometer". The supports of the apparatus are fixed to the table frame by two clamps for each support. The apparatus includes two hooks which are made of hardened steel. Each hook is fixed by a sealed loop device to a 10-strand steel wire with hemp core. The wire on the left side is attached to a device with a screw to take up the wire slackness while that on the right runs over two pulleys mounted on ball bearings to minimize friction. The right wire ends at another pulley to which a handle is attached. The pulley is connected to loading compression springs with a common calibrated scale to read the load in pounds. The mechanism is fitted with a special non-return ratchet to maintain the applied force while loading and can be used for quick unloading. The device for taking up the wire slackness which lies on the left side as well as the first pulley which lies on the right side are both fixed to slots which allow up and down movement according to the distance between the surface of the table and the level of the symphysis pubis so as to keep the traction in a horizontal direction and thus practically avoiding any angle of error.

Choice of Material and Technique

For the sake of proper comparison, all bodies studied post mortem were of the age group twenty-five to forty years, and all were of average body build (debilitated and old bodies were excluded). The pregnant bodies autopsied included primigravidae and multigravidae.

The ligament to be studied was left intact while all others were severed. The hooks were applied on either side around the superior pubic ramus into the corresponding obturator foramen. The handle was worked very gradually and the reading at the moment of rupture of the ligament was recorded. Ten bodies of each type were used for the study of each ligament and the average was taken; that means forty tests were made on each ligament in four groups.

Results

A. *Anterior ligament* (Table I)

B. *Inferior ligament* (Table II)

C. *Superior ligament* (Table III)

The different ligaments of the symphysis pubis in males are generally much stronger than those

Table I

A. Anterior Ligament

													Average (Pounds)
Men	650	800	750	600	650	500	650	600	700	850	675
Nulligravidae	500	600	550	500	650	500	600	550	550	500	550
Multiparae (not pregnant)	550	500	600	450	650	500	500	550	600	450	535
Pregnant women (last 3 months) ..	350	450	300	500	450	350	250	400	350	200	360

Table II

B. Inferior Ligament

													Average (Pounds)
Men	600	450	550	600	500	450	400	400	350	400	470
Nulligravidae	400	300	350	350	400	250	300	300	450	250	335
Multiparae (not pregnant)	450	250	250	300	350	300	250	200	200	450	300
Pregnant women (last 3 months) ..	200	300	300	250	200	300	200	350	250	250	260

TABLE III

C. Superior Ligament

											Average (Pounds)
Men	300	350	300	400	350	250	300	250	400	350	320
Nulligravidae	350	200	200	350	300	200	200	250	300	200	255
Multiparae (not pregnant)	200	200	250	350	150	300	250	300	150	250	235
Pregnant women (last 3 months) ..	150	200	300	200	150	100	300	150	200	150	190

of females. The strength of the different ligaments in females is not affected by having borne children, but they are weakened during the last three months of pregnancy. The weakening of the anterior ligament is much greater than that of the other ligaments. This is probably attributable to the fact that the anterior ligament is strengthened by the medial tendons of origin of the two recti muscles as well as by the fibres of the external oblique aponeuroses, all of which are unduly stretched during the last three months of pregnancy.

The above results might to some extent help to explain the variations of the conditions under which our reported cases of ruptured symphysis pubis occurred.

CASE REPORTS

Case 1. Multipara, aged thirty-eight years, pregnant 9 months, suffered from sudden rupture of symphysis pubis with consequent wide separation of 4 centimetres (X-ray) as a result of coughing. The condition was simultaneously complicated by severe left sacro-iliac strain suggesting an associated rupture of the corresponding anterior sacro-iliac ligament. She was delivered by Caesarean section and a tight corset was advised. Complete recovery took place in about three months.

Case 2. Second-gravida, twenty-four years of age. She had had a history of a difficult forceps during the first delivery which was complicated by rupture of the symphysis pubis during the operation. During the second pregnancy, she attended at the seventh month with a gap of three centimetres (X-ray). A corset was advised. She was seen late in the second stage of labour and was delivered spontaneously without injury.

Case 3. Primigravida, aged thirty years. She was delivered normally at the hospital and was discharged in a normal state eight days after delivery. On entering her home, she slipped and, trying to recover her balance' felt a sudden painful snap at the symphysis pubis. She had to be carried to bed. The inter-pubic space showed a gap of three centimetres (X-ray). A tight corset was advised. Healing was complete after three and a half months, and the inter-pubic space returned to normal.

Six cases of symphysiotomy were attended by one of us (A.I.) during the years 1940 to 1943, when the late Professor Shafik tried to revive this operation by cutting the anterior ligament and applying his own apparatus for forcible gradual separation. In 5 the operation was very successful. In the sixth case, the remaining ligaments ruptured suddenly during operation and the gap increased to 5 centimetres. This was accompanied by involvement of the left sacro-iliac joint. There was injury to the left sacral roots with paralysis and paresis. The patient recovered very gradually and left hospital after six months with residual paresis. In all the other cases of symphysiotomy in which the separation did not exceed 4 centimetres there was no sacro-iliac involvement.

SUMMARY AND CONCLUSIONS

(1) A mechanical study of the different ligaments of the symphysis pubis was carried out using a specially devised apparatus "Pubic Symphysiometer". This shows the changes which occur due to parity and the pregnant state. The anterior ligament was observed to be much more weakened during the last three months of pregnancy than other ligaments. The ligaments can regain their original strength after child-bearing, as evidenced by the comparison between the

different ligaments of nulliparae and non-pregnant multiparae after involution.

(2) Three cases of rupture of the symphysis pubis are presented and 6 cases of symphysiotomy recorded. It is observed that rupture of the symphysis pubis is a very rare accident, estimated to occur once in every 2,000 deliveries. Multiparity does not particularly predispose to it. The accident is not dangerous to life and vaginal delivery is safe so long as the sacro-iliac joints are not involved. The condition can be very successfully treated by a corset, and surgical interference or wiring of the symphysis pubis is unnecessary.

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SODIUM METABOLISM IN GYNAECOLOGY AND OBSTETRICS

BY

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I.—NON-PREGNANT WOMEN

SODIUM is the main cation in the extracellular fluid. It plays a very important role in the constancy of the milieu interieur and the maintenance of its concentration within physiological limits is essential for the activity of nervous and muscular systems. The constancy of the osmolarity of the extracellular fluid is essential for the cellular metabolism. Sodium is the cation that is responsible for retaining the body water and hence determines the size of the extracellular space. The kidney uses sodium ions to regulate the pH of the body. The different aspects of the physiology of sodium have only recently been discovered and explored. In the light of this new knowledge many clinical problems have been re-examined. It has been realized that disturbances in its metabolism can be detrimental and even fatal.

The subject is very big. The first part of this paper is meant only to cast a light on a few points and to pave the way to the discussion of the relationship between sodium and pre-eclampsia.

PROPER UNDERSTANDING OF MODERN EXPERIMENTAL TECHNIQUES

The study of sodium metabolism in recent years has been mainly carried out using radioactive tracers. They have proved to be the ideal method for the study of the problem.

(1) *Exchangeable Sodium, Na_{Ex}*

Before the use of radio-isotopes our information was obtained from balance studies, which can tell us what is going into, what is coming out of, but never what is present in the body.

The use of radio-isotopes has enabled us to determine the physiologically active part, i.e., the fraction which exchanges quickly with the radioactive tracer dose. Isotope techniques do not measure the remainder of body sodium which is only potentially active and stored as it were in bone.

(2) *24-hour Exchangeable Sodium*

The expression Na_{Ex} must always be related to time. The values of 8-hour or 36-hour measurements are different. Twenty-four-hour exchangeable sodium is used because most of the exchangeable sodium in the body mixes with the tracer dose after 24 hours and because it is convenient for clinical work.

(3) *Total 24-Na_{Ex} and 24-Na_{Ex}/kg.*

In any scientific discussion the term Na_{Ex} must be either preceded by "total" or followed by "/kg.". More than one example can be found in the literature where the whole discussion is confused as is the reader, by the use of the unqualified term Na_{Ex} in both contexts. The following example illustrates the difference between them.

A person starts to put on weight in the form of muscle. The exchangeable sodium is measured before and after the weight increase. A comparison of the levels of total exchangeable sodium will show an increase due to the amount of sodium retained in the new muscles. Comparison of the Na_{Ex}/kg. levels before and after the weight increase should show no difference because the extra retained sodium will be proportional to the weight increase.

(4) *Sodium Space*

Sodium space has nothing to do with sodium metabolism. Sodium space is supposed to mean or to give an approximate figure of the size of the extracellular space. An increase in sodium space may very well be associated with normal or even less than normal Na_{Ex}/kg.

(5) *Sodium Retention*

It seems that the use of the word "retention" always has pathological significance. A pregnant woman retains sodium for the development of the foetus. This is a physiological process and there is no mystery about it. If more than the quantity of sodium that is required for this purpose is retained by a pregnant woman, then this should be called abnormal sodium retention.

Distribution of Sodium in the Body

A human body weighing 70 kg. contains 5,000 meq. of sodium. The bones contain 3,000 meq. of which only 1,000 meq. are exchangeable. Apart from skeletal sodium the remaining 2,000 meq. are all exchangeable and are distributed as follows:

1,500 meq.	extracellular
200 meq.	intracellular
300 meq.	gut contents
2,000	

The average daily intake is 100 meq. and in a balanced person the same amount is excreted every day mainly through the kidney (Munroe, 1959). These figures are easy to remember but they apply to a person weighing 70 kg. The average weight of British non-pregnant women is 55 kg. according to Thomson and Billewicz (1957) who analyzed 4,124 cases. The sodium content of such an average non-pregnant woman is 3,900 meq.

Bone and Sodium Metabolism

Bone, which has always been considered merely a supporting structure, is now known to be an active participant in physiological processes concerned with electrolyte metabolism.

Kaltreider and his colleagues (1941) calculated that one-third of total body sodium is present in bones, a figure which is in close agreement with the fundamental work of Harrison, Darrow and Yannet (1936) who employed classic analytical methods. Kaltreider *et al.* also discovered that only 35 per cent of total body sodium is exchangeable with ^{24}Na after 24 hours.

The precise chemical association of sodium in bone is not known. There is good evidence to support the hypothesis that this cation is present at the crystal surface as a double salt of carbonate: Ca-O-CO_3-Na.

The skeleton comprises a large mineral mass deposited in or on a collagenous ground substance. The electrolytes of the mineral mass are in dynamic equilibrium with ions in surrounding extracellular fluid. The Bone Bank, as Owen (1952) calls it, stabilizes serum Ca and Mg concentrations and contributes substantial amounts of Ca, K, Na and CO_3 to the base economy of the body during periods of stress (Owen, 1952).

The mechanism which governs this blood-bone equilibrium has been revealed by Albright and Reifenstein (1948) to be endocrinal in the case of calcium. This may prove to be the case with other cations.

So the skeletal system is not only the supporting frame of the human being and the shelter of the haemopoietic system but also a great mineral reservoir for the body.

Relation of Age to Na_{Ex}

Edelman *et al.* (1954), reviewing the available figures and adding their own, classified the data according to age groups. They found that whether in men or in women Na_{Ex}/kg. is the same in different age groups. MacGillivray *et al.* (1960) confirmed these results.

Sex and Na_{Ex}

Edelman *et al.* (1954) compared male and female figures. He found a difference of 2·9 meq./kg., but this was not statistically significant.

What is the Normal Average Na_{Ex}/kg.?

41 ± 5 meq./kg. is the figure which was taken by Edelman *et al.* (1954) to represent a normal

standard reference for human adults. The figure is quite acceptable and agrees with the results of other workers (Forbes and Perley, 1951; Warner *et al.*, 1952; Miller and Wilson, 1953; MacGillivray *et al.*, 1960).

Equation to Predict Total Na_{Ex}

As the Na_{Ex} content/kg. is the same in adults of any age whether male or female MacGillivray *et al.* (1960), using the above figure for Na_{Ex}/kg., adopted the following equation:

$$\text{Total } Na_{Ex} = 67\,W - 7398\,R + 1233$$

W = weight in kg.
H = height in cm.
R = W/H

SODIUM AND THE MENSTRUAL CYCLE

The difficulty in studying such a problem is that there is no agreement about the range of normality. Some consider a certain degree of pain to be only discomfort and other associated symptoms normal while others consider them to be dysmenorrhoea or pre-menstrual tension.

Morton (1950) found variable changes in serum Na and K during the menstrual cycle with a tendency to lower level before menstruation which he attributed to increased water retention.

Using ^{22}Na Ansell and Clarke (1956) compared men and women. The biological half life of ^{22}Na in men was 9–10 days while in women it was spread over a range from 9–21 days showing retention during the menstrual cycle in at least some of them.

In 1957 Klein and Carey by repeated estimations of total Na_{Ex} using ^{22}Na came to the conclusion that there was no significant relation between Na_{Ex} and the menstrual cycle.

Chesley and Hellman (1957) found that sodium retention was not maintained during the pre-menstrual period even when a woman was put on high sodium intake.

SODIUM RETENTION AS A CAUSE OF PRE-MENSTRUAL TENSION

Recently there has been evidence supporting the suggestion that abnormal sodium retention is an important aetiological factor.

(1) The symptoms of pre-menstrual tension are mainly nervous: headache, irritability, depression, insomnia, nausea and vomiting. In a recent paper by Gibbons (1960) a direct relation between Na_{Ex} retention and symptoms of depressive psychosis was found. The same relationship was found in recurrent schizophrenia (Schottstaedt *et al.*, 1959).

(2) A marked increase in urinary excretion of aldosterone in pre-menstrual tension was reported recently by Prunty (1959).

(3) Prunty (1959) attributes the good results obtained when treating pre-menstrual tension with progesterone to its marked natriuretic effect.

II.—PREGNANT WOMEN

In any anabolic process there is always retention of the necessary substances required for building a new tissue: nitrogen, water and potassium for cellular elements, water and sodium for the associated extracellular space. The most outstanding example of such anabolic process is pregnancy.

What is the Amount of Sodium Necessary for Pregnancy?

The extra amount of sodium retained during pregnancy is required partly by the foetus and partly by the mother for the development of the uterus, placenta and for expansion of the extracellular space. This amount was calculated by Gray and Plentl (1954) as 510 meq. Na_{Ex}, that is 12 g. Na, and by Rhodes (1960) as 20·5 g. Na_{Ex} as follows:

Foetus	5
Liquor amnii ..	2·3
Breasts and placenta	3·6
E.C.F.	7·6
Uterus	2·0
	20·5 g. Na_{Ex}

These figures were obtained by simple calculations from different sources of information. They remained to be checked by experimental work. So the next question arises.

How Much Na_{Ex} is Retained During Pregnancy?

Gray and Plentl by repeated estimations on the same group of patients found that each retained 510 meq. MacGillivray and Buchanan's figure (1958) was 756 meq. of Na_{Ex}. These figures agree with what is to be expected by theoretical calculation within the range of experimental error. Is this the only amount of sodium retained?

The figures of sodium retention during pregnancy obtained by balance studies were variable but on the whole higher than those of Na_{Ex} (Coons *et al.*, 1934; Hummel *et al.*, 1936; Freyberg *et al.*, 1938; Taylor *et al.*, 1939; Chesley, 1944). Chesley (1944) suggested a figure of 3 g./week. According to these figures, if sodium retained is osmotically active, at least 28 litres of water would collect in the body, which is not the case. The only available explanation is that the difference between total sodium retained and that retained in an exchangeable form is stored in an inactive form in the bone bank.

Sodium Economy in Normal and Abnormal Pregnancy

In the last ten years many workers have developed an interest in the problem. I think a comparative study of the results of three pairs of workers will cover the current divergent ideas (Gray and Plentl, 1954; Plentl and Gray, 1959; Dieckmann and Pottinger, 1957; MacGillivray and Buchanan, 1958).

It is wiser to discuss the question in normal and in toxaemic patients separately.

(1) *Normal Pregnancy*

Dieckmann and Pottinger (1957) concluded that during normal pregnancy the body retains 10 per cent more Na_{Ex} than non-pregnant women but the figures related to kg. body weight were 42·3 meq. and 40·2 meq. in the non-pregnant and in the normal pregnant respectively.

MacGillivray and Buchanan (1958) also investigated the problem. They found an increase from 41·5 meq. Na_{Ex}/kg. in non-pregnant state to 48·3 meq. Na_{Ex}/kg. during normal pregnancy. They concluded that these figures confirmed that there was retention of 755 meq. Na_{Ex} during pregnancy. This amount is equal to that required to retain the extracellular water in the products of conception. Thus in normal pregnancy there is storage of Na_{Ex} and water in the correct proportions.

Plentl and Gray (1959) who were always interested in water and electrolytes in obstetrics investigated the problem again. They estimated Na_{Ex} in 16 pregnant and 16 non-pregnant women. The average figures were 40·2 meq. Na_{Ex}/kg. and 39·6 meq. Na_{Ex}/kg. respectively. They also concluded that the amount retained of Na_{Ex} is equal to what is required for foetal development. Table I summarizes these results.

Table I

Exchangeable Sodium in Normal Women

Author	Na_{Ex}/kg.	
	Non-Pregnant	Normal Pregnant
Dieckmann and Pottinger, 1957	42·3	40·2
MacGillivray and Buchanan, 1958	41·5	48·3
Plentl and Gray, 1959	40·2	39·6

Discussion

The number of patients investigated was not mentioned in Dieckmann and Pottinger's paper and there was no statistical control for their results, but the difference between Na_{Ex}/kg. in non-pregnant and pregnant women was small. Their results agree with those of Plentl and Gray.

Comparing Plentl and Gray's results with those of MacGillivray and Buchanan it is interesting that they came to the same conclusions from different figures.

The question to be answered is: If a pregnant woman retains what is necessary for the products of conception, will there be any difference in the Na_{Ex}/kg.?

As the patient who is retaining sodium is also gaining weight at the same time one would expect no significant difference in the Na_{Ex}/kg. That was the case in Plentl and Gray's and Dieckmann and Pottinger's results.

In spite of the fact that the figures of MacGillivray and Buchanan regarding Na_{Ex}/kg. were contradictory to both the others, the results of the three present the same answer: that is, *in normal pregnancy there is no abnormal retention of exchangeable sodium and all that is retained is accumulated in the products of conception.*

(2) *Pre-eclampsia*

Until 1958 most work tended to prove the existence of abnormal sodium retention in pre-eclampsia. At the same time restriction of sodium in diet, which was originally advocated by de Snoo and Remmelts (1938), was almost the rule in most centres. Two papers appeared which attracted much attention.

The first was a properly-controlled study by Robinson (1958) using 2,019 patients. She found extra salt in diet essential for the health of the pregnant woman and her child. She treated twenty patients with early pre-eclampsia with extra salt; all of them improved.

It is interesting to read the comment of Eastman (1958) on this paper. He wrote: "To the modern obstetrician the contention set forth in this paper will appear a good deal like claiming that the best way to treat strychnine poisoning is to give the patient more strychnine. To say that it upsets all our concepts about the etiology and the treatment of the toxemias is an understatement. Indeed, if this contention is valid we shall have to throw all our books out of the window and rush some new ones through the press recommending a high salt diet in pregnancy."

The second paper, by MacGillivray and Buchanan (1958), showed a statistically significant difference between normal and toxaemic women but in the opposite direction. There is less Na_{Ex}/kg. in toxaemic patients than in normal pregnant women. There was also no relation between the severity of pre-eclampsia and Na_{Ex}/kg. There is no doubt that this paper aroused great interest in the subject and stimulated further work.

In the light of these new ideas and of previous experience we started to re-investigate* the same problem and to see if in pre-eclampsia there is any abnormal retention of Na_{Ex} or not.

* This work was made possible by a research grant from the Royal Infirmary of Edinburgh.

Choice of Material

The study included 65 pregnant women (36 non-toxaemic and 29 toxaemic) admitted as in-patients to the Simpson Memorial Maternity Pavilion, Edinburgh, in the third trimester. There are two important points regarding the choice of toxaemic patients and the normal controls.

The first is that realizing the different points of view given on this subject in recent literature, we decided to avoid borderline cases. Every clinician is aware of the problem of pregnant women who show a slight rise in blood pressure reading. Some consider them to be cases of mild pre-eclampsia while others prefer to call them hypertension in pregnancy. The distinction may be very difficult and many accept that the presence of slight oedema is evidence that the diagnosis is pre-eclampsia. To avoid this confusion every patient included in this series as a case of toxaemia had a blood pressure of at least 150/90 with either oedema or albuminuria or both.

The normal controls were 36 patients admitted to the ward for observation as in cases of previous Caesarean section or other minor ailments which have no effect on water or electrolyte metabolism. As it has been pointed out previously (Gray and Plentl, 1954; Mahran, 1960; Davey, 1960) that metabolic disturbances may appear before clinical symptoms, we considered it essential that no normal control should be included in a comparative study before she had been followed up through pregnancy and labour. Any patient who later developed any sign or symptom of pre-eclampsia was excluded.

Method

Each patient drank 30 μc ^{24}Na diluted with milk after emptying her bladder. Her weight and height were recorded. All the urine passed during the subsequent twenty-four hours was kept in a polythene container. This is referred to as pooled urine (Up). Half an hour later the bladder was again emptied. This is called

TABLE II

Exchangeable Sodium in Pregnant Women

Type	Number of Cases	Na_{Ex} meq/kg.				
		Mean	Standard Deviation	t	P	Significance
Normal	36	43	5·1	2·67	·01	+
Pre-eclamptic	29	46·2	4·2			

the Spot specimen (Us). Immediately after 20 ml. of venous blood were withdrawn and sodium content estimated by flame-photometer.

The radio-activity was estimated in a well scintillation counter of both (Up) and (Us). The total exchangeable sodium is calculated as follows:

$$\text{Total } {}^{24}Na_{Ex} = \frac{\text{Activity administered} - \text{Activity excreted (Up)}}{\text{Activity in body (Us)}} \times \times \text{Na meq. in plasma.}$$

Then the figure is expressed as meq. Na_{Ex}/kg.

RESULTS

It is clear from Table II that a significant difference does exist. In pre-eclampsia there is abnormal retention of Na_{Ex} in the body.

DISCUSSION

Table III summarizes the results of this and previous work.

It seems that there is agreement among most workers that in pre-eclampsia there is abnormal content of Na_{Ex} in the body.

TABLE III

Author	Meq. Na_{Ex}/kg.	
	Normal Pregnant	Pre-eclamptic
Dieckmann and Pottinger (1957)	40·2	44·9
MacGillivray and Buchanan (1958)	48·3	43·8
Plentl and Gray (1959)	39·6	46
This paper (1961)	43	46·2

Working from another angle Chesley and Hellman (1957) and Chesley (1960) proved that in pre-eclampsia there is a reduction in glomerular filtration rate and an increase in tubular re-absorptive capacity which would provide a reason for salt retention. It was found that this abnormal retention is related to the severity of the condition (Moore, 1957). Others found that this biochemical disturbance continues to a certain extent in the early puerperium (McCartney *et al.*, 1959). A significant difference was also found in figures of Na_{Ex} related to lean body mass estimated by densimetric methods (McCartney *et al.*, 1959). Hutchinson and Plentl (1954) drew attention to an interesting point. When they were following their patients with repeated estimations of total Na_{Ex} they found that an abnormal Na_{Ex} retention was observed in one patient who later developed pre-eclampsia before any of the clinical signs appeared. Recently this was confirmed in a bigger series by Davey (1960) who included 103 unselected primigravidae 11 of whom developed pre-eclampsia.

CONCLUSION

It seems therefore that there is agreement upon one aspect of this problem and that is that there is abnormal sodium retention in pre-eclampsia. All the work hitherto done with few exceptions gives only a static aspect of the picture. The importance of the next step was stressed by Kellar (1960) and that is the need for a dynamic picture of the changes which take place during the development and progress of pre-eclampsia. Such studies will enable us to understand when the retention of sodium occurs,

when re-excretion takes place and the relation of sodium metabolism to various degrees of severity of the disease.

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INTRA-PARTUM ASPHYXIA

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IN an analysis of the classification and causes of perinatal mortality (Bound, Butler and Spector, 1956) intra-partum asphyxia was defined as death during labour or shortly after birth, with evidence of asphyxia and with no other apparent cause of death. Nearly one-third of stillbirths occur during labour as a result of trauma or asphyxia. Foetal death during labour would seem to be the most promising field for reducing perinatal mortality by improved obstetrics. Birth trauma is often inflicted in an attempt to deliver an asphyxiated baby *per vaginam* and the increased use of Caesarean section in this hospital has resulted in a satisfactory reduction in the incidence of birth trauma. However, the incidence of intra-partum asphyxia has increased slightly during this period. These trends are probably reflected elsewhere in Great Britain. We have therefore analyzed the last one hundred deaths occurring as a result of asphyxia in labour from the clinico-pathological viewpoint. We have also classified deaths as potentially avoidable when retrospective study of the case indicated that alternative management might have prevented foetal death.

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TABLE I

Category	Number	Incidence/ 1,000 Births
All births	14,948	—
Stillbirths	311	20·8
Intra-partum asphyxia ..	100	6·7
Hypertension in last trimester	1,455	96·9

The material was taken from the deliveries occurring in the Obstetric Unit, University College Hospital, between 1st January, 1949 and 1st May, 1960. Table I shows that during this time there were 14,948 deliveries, of which 311 were stillborn. The overall incidence of hypertension (blood pressure greater than 140 mm. Hg systolic or 90 mm. diastolic) during the last trimester was 9·69 per cent. This includes cases of toxaemia and essential hypertension.

RESULTS

An autopsy was performed on all infants and these cases were discussed jointly by pathologist, paediatrician and obstetrician. A diagnosis of intra-partum asphyxia was made when pleural and pericardial haemorrhages and other signs of

asphyxia (see below) were found in a baby that died during labour or shortly after birth with signs of asphyxia for which no other cause for death could be found. The foetal heart had been heard at the onset of labour in 87 cases. In 13 cases the baby was already dead on admission to the labour ward, but showed no evidence of maceration at autopsy and was therefore considered to have died during early labour.

TABLE II

Pathological Findings in 74 Stillbirths and 26 Neonatal Deaths from Intra-partum Asphyxia

	No.
Asphyxial haemorrhage on pleura	100
Meconium in airway	22
Massive inhaled debris	15
Subarachnoid haemorrhage	11
Tentorial fraying or a tear	10
Haemoperitoneum	3
Baby less than 2,500 g. after 37/52 gestation	23
Placenta less than 400 g. after 37/52 gestation	14
Baby more than 4,000 g.	5

Table II shows the pathological findings in the 26 neonatal deaths and 74 stillbirths examined. Gross meconium in the airway was found in 22 cases, with a slightly higher incidence in babies dying shortly after birth (27 per cent as opposed to 20 per cent). A further 15 infants showed considerable amounts of solid material in the alveoli on microscopic examination of the lungs. From this it can be inferred that excessive respiratory movements by the foetus during labour occurred in at least one-third of our cases of intra-partum asphyxia. Eleven babies showed focal subarachnoid haemorrhages and 10 showed evidence of traumatic delivery (fraying or tearing of the tentorium). In none of these cases was birth trauma considered the principal cause of death. Haemoperitoneum due to rupture of a subcapsular haematoma on the surface of the liver was present on 3 occasions. The weight of the baby was considerably less than average for the period of gestation in 23 cases, and in 14 this was accompanied by a small placenta. No attempt has been made in this series to assess the amount of placental infarction. In 5 cases the baby was considerably larger than average.

Other pathological findings which could be regarded as associated with asphyxia were as follows: pulmonary oedema, 2 cases; pleural effusions, 2 cases; emphysema, 2 cases (both neonatal deaths); suprarenal haemorrhage, 1 case; pneumonia, 2 cases (both slight); inhaled blood, 1 case; marks of uterine constriction ring, 1 case; and meconium peritonitis due to rupture of the colon, 1 case.

Clinical Associations

Table III shows the initial subdivision of the cases into clinico-pathological groups associated with particular aetiological features. It can be

TABLE III

Analysis of 100 Cases of Intra-partum Asphyxia

Major Aetiological Factor	All Cases		Cases of Toxaemia	
	No. of Cases	Potentially Avoidable Cases	No. of Cases	Potentially Avoidable Cases
Abnormal labour	24	11	6	2
Premature separation of normally situated placenta	17	3	9	3
Postmaturity	20	20	15	15
Toxaemia	15	8	15	8
Multiple pregnancy	9	5	4	3
Placenta praevia	7	1	4	1
Maternal disease in labour	6	2	1	1
Uncertain	2	1	0	0
Total	100	50	54	33

TABLE IV
Analysis of 25 Cases of Abnormal Labour

Abnormality in Labour	No.	Toxaemia	Potentially Avoidable
Cord prolapse in vertex presentation	6	2	2
Cord prolapse with malpresentation	3	0	2
Premature breech delivery	6	2	0
Malpresentation	3	0	1
Difficulty with shoulders	2	1	2
Disproportion with trial of labour	2	1	2
Long labour	2	0	2

seen that most of the potentially avoidable cases occurred in women with toxaemia, postmaturity or abnormalities of labour.

Abnormal labour. Table IV shows the factors in abnormal labour which we have considered as contributing to foetal death from intrapartum asphyxia. Prolapse of the cord occurred 6 times with vertex presentations and 3 times with malpresentation (two breech and one transverse lie). Premature breech delivery, with an average foetal weight of 1,500 g., occurred 6 times and in 5 cases was associated with premature rupture of the membranes before the onset of labour. It may be that in these cases prolapse of the cord occurred without being diagnosed.

Malpresentation alone was considered to be an aetiological factor in 3 cases, a transverse lie, a shoulder presentation and a persistent occipito-posterior. Undue delay in delivering the shoulders occurred twice; both babies weighing more than 4,000 g., one from a diabetic mother. Borderline cephalo-pelvic disproportion was considered to be the cause of foetal death on two occasions, one with trial of labour for a high head at term and one with deep transverse arrest. Prolonged labour was considered a factor in 2 cases, labour lasting three and five days with the development of maternal distress in both cases.

Premature placental separation. Premature separation of a normally situated placenta occurred in 17 cases. This diagnosis was made when ante- or intra-partum haemorrhage occurred with no evidence of placenta praevia. In 8 cases the blood pressure was normal, and of these 8, 6 presented with intra-partum haemorrhage. In the remaining 9 cases with elevated blood pressure, 8 presented with the picture of abruptio placentae. This group, of course, represents those cases of abruptio placentae in which the foetus was still alive on admission to hospital and therefore a potential live birth.

Postmaturity. This was considered to be present at the end of the fortieth week of gestation. Cases in which there was uncertainty over dates are not included. This date was chosen to emphasize the danger of any degree of postmaturity in association with toxaemia. In all 20 deaths occurred during labour after a gestation of more than 40 weeks. As shown in Table V, the commonest associated factor was a raised blood pressure, which was present in 15 cases. Trial of labour for disproportion was undertaken in 3 cases, one of which also had toxaemia and is included in the toxaemia group as well. In one case the mother's age was forty-four, and in another case pyrexia early in labour occurred. There was one case in which no explanation other than postmaturity could be found.

TABLE V
Analysis of 20 Cases of Postmaturity

Associated Factors	No.
Toxaemia	15
Trial of labour for cephalopelvic disproportion	3
Maternal age over 40	1
Pyrexia in labour	1
Nil	1

It would seem, therefore, that postmaturity by itself is not commonly associated with death of the foetus during labour, but that when other abnormalities, in particular toxaemia, are present, the risk of foetal death is considerably increased.

Toxaemia. The total number of cases with toxaemia was 54, and in 17 cases the diastolic blood pressure was greater than 100 mm. In 15 cases, foetal death occurred in labour in women with toxaemia and no other complication. In 39 cases toxaemia was accompanied by some other additional factor contributing to foetal death. The most important of these were postmaturity (15 cases) and premature separation of the placenta (13 cases including those where the placenta was praevia).

Multiple pregnancy. Intra-partum asphyxia occurred in 9 cases of twin pregnancy. In 8 cases one twin survived, and in one case both twins died. In view of the complexity of the situation, no attempt has been made to allot cases in this group to other clinico-pathological states. Toxaemia was present in three cases, two of which were also postmature. Two cases of undiagnosed twins occurred in which ergometrine was given intravenously with the crowning of the first head. There was one case of prolapsed cord, and three cases in which no aetiological factor other than multiple pregnancy was discernible.

Placenta praevia. This was diagnosed in 7 patients, four of whom also had toxaemia.

Maternal disease in labour. Maternal diseases present in labour were: *Escherichia coli* septicaemia following artificial rupture of membranes, anaphylactic shock due to penicillin given prophylactically to the mother for prolonged rupture of membranes, acute bronchitis, appendicitis with appendix abscess, agranulocytosis due to chloramphenicol and active rheumatic endocarditis with superimposed bacterial endocarditis.

Uncertain group. In only two cases of the hundred analyzed was there no aetiological factor which could reasonably be held responsible for foetal death. It would seem that completely inexplicable foetal death during labour is rare in this hospital.

Potentially Avoidable Deaths

Deaths were placed in this category when retrospective analysis of the case records showed that alternative management might have saved the baby. Table VI shows that a potentially avoidable factor was present in half the cases. The commonest potentially avoidable factor was undue prolongation of pregnancy in women with toxaemia. In 15 cases women with raised blood pressures were delivered after the forty-first week. The remaining 6 cases were women with severe toxaemia delivering before term, in which no action was taken to terminate pregnancy despite clear signs of deterioration. The other major avoidable factor was failure to effect delivery within an hour in the presence of unequivocal foetal distress, i.e., slowing or irregularity of the foetal heart with or without meconium-staining of the liquor. This occurred in 15 cases. Failure to diagnose complications of labour occurred six times; these were two cases of undiagnosed twins, one unrecognized transverse lie, one unrecognized prolapsed cord, one failure to listen to the foetal heart in a

TABLE VI

Analysis of Distribution of Avoidable Factors

Avoidable Factor	No. of Cases
Undue prolongation of pregnancy in toxaemia	21
Failure to accomplish delivery promptly in the presence of foetal distress	15
Failure to diagnose complications of labour	6
Postmaturity with abnormalities	4
Mismanagement of long labour	2
Failure to treat maternal disease in labour	2
Total	50

TABLE VII

Analysis of Signs of Foetal Distress

Manifestations of Foetal Distress	Number
Increase in heart rate >160	9
Slowing of heart rate <120	13
Passage of meconium	9
Passage of meconium+altered heart rate	10
Foetal heart absent on admission	13
No signs of foetal distress detected with stillborn foetus	34
No signs of foetal distress—live birth but dying shortly after birth with evidence of asphyxia	12

woman with toxaemia, and one case of unrecognized abruptio placentae.

The presence of complicated labour with postmaturity was considered an avoidable factor in 4 patients; these were three cases of trial of labour for cephalopelvic disproportion and one breech delivery of a baby weighing 5,100 g.

Mismanagement of prolonged labour was considered to be an avoidable factor in 2 cases, labour lasting three and five days with development of maternal pyrexia and tachycardia. Failure to treat maternal disease in labour occurred twice; an unrecognized appendix abscess and one case of *E. coli* septicaemia following artificial rupture of the membranes.

Foetal Distress

The manifestations of foetal distress in this series of one hundred cases are given in Table VII. In 13 cases the foetus was already dead on admission. The commonest indication of foetal distress was some change in heart rate. However, of the 87 cases in which the baby was known to be alive on admission to hospital, in 34 no evidence of distress was detected although the baby was stillborn. In a further 12 cases in which foetal distress was not detected the baby was born alive but died shortly after birth with signs of asphyxia. It is probable that most, if not all, asphyxiated babies will have changes in foetal heart rate during the agonal phase. FitzGerald and McFarlane (1955) found that foetal distress was present in most cases of babies dying during labour when the foetal heart was adequately recorded. It would seem that increased attention to the foetal heart in women with toxaemia or with abnormalities in labour would result in increased diagnosis of foetal distress, and perhaps an increased foetal salvage.

DISCUSSION

The work of James (1960) indicates that normal birth is accompanied by biochemical evidence of considerable anoxia, as judged by accumulation of lactic acid and the development of acidosis in the newborn infant in the first hour after birth. It is clear from the present investigation that foetal death during labour, for which no cause can be found, is uncommon. This is in contrast to the findings of FitzGerald and McFarlane (1955) who were unable to suggest any explanation for 20 per cent of cases in a series of 45 deaths during labour. The human foetus, like most newborn mammals, is highly resistant to oxygen lack. It can probably survive undamaged at least twenty minutes of total anoxia. This tolerance is not exceeded during normal labour. Nevertheless, any factors compromising oxygen supply will be associated with an increased risk of foetal death during labour.

Premature separation of the placenta, prolapse of the cord, disproportion and long labour are all well recognized in this respect and need no further comment. However, a large proportion of stillbirth due to asphyxia during labour is not associated with mechanical factors. In the past such cases have often been attributed to unknown causes. It appears from the present investigation, however, that most of these "non-mechanical" deaths may be due to inadequate placental reserve.

Both toxaemia and postmaturity are said to be associated with reduced umbilical artery

saturation and polycythaemia of the cord blood (Walker, 1959). These findings have been interpreted as evidence of "placental inadequacy". However, the polycythaemia may well be due to haemoconcentration and the range in umbilical artery oxygen saturation is very wide, even in normal births. Other workers have been unable to confirm Walker's findings.

The fundamental disturbance responsible for the increased perinatal mortality in toxaemia is considered to be a reduction in maternal blood flow through the intervillous space (Browne and Veall, 1953). This is confirmed by the reduction of myometrial radio-sodium clearance in toxaemia (Morris, Osborne and Wright, 1955). Recently Dixon and Robertson (1958) have shown obliterative changes in the arterioles supplying the placental bed in toxaemia, which could well be responsible for inadequate placental perfusion. The definite association of extensive true infarction of the placenta with severe toxaemia is further evidence of placental ischaemia (Little, 1960).

A further factor influencing the blood supply of the placental site is the sensitivity of the blood vessels to vasoconstrictors. Martin and Young (1960) have shown that the amount of adrenaline needed to produce experimental foetal distress in the guinea-pig decreases progressively towards term and that treatment with oestrogen and progesterone modifies this.

The combination of postmaturity and hypertension is well known to be unfavourable to the foetus (Walker, 1954; Martin, 1955; Bound *et al.*, 1956). Postmaturity itself has often been suggested as a contributory factor in "placental inadequacy" but the evidence for this is not very satisfactory. In our cases we found only one instance in which uncomplicated postmaturity was the only discoverable aetiological factor. At present it is the policy of this department to induce cases of postmaturity only under the following circumstances: (1) a raised blood pressure, (2) over 30 years of age, (3) multiple pregnancy, (4) breech presentation (legs extended), (5) previous ante-partum haemorrhage, (6) previous stillbirth, (7) false labour. The remaining cases are allowed to go into spontaneous labour.

In the present investigation toxaemia was considered to be the major cause of death from intra-partum asphyxia in 30 cases, of which half were postmature. The measurement of placental adequacy is not possible in retrospect, but in 14 of these thirty cases the foetal or placental weight and in some cases both was considerably less than that expected from the duration of gestation. Twelve of these fourteen cases were recognized in the last trimester as being "small for dates". FitzGerald and Clift (1958) have suggested that labour is a considerable risk in these "starveling" babies. The weight of the placenta is not always a reliable guide to the amount of functioning trophoblast, as it is possible that a placenta of apparently normal weight may be inadequate because of severe infarction.

Little (1960), in an analysis of 1,000 unselected placentae, made quantitative measurements of the amount of infarcted placenta. He concluded that the "placental reserve" is not as large as has been suggested, and that it is reduced in toxaemia. During labour there is probably intermittent focal ischaemia of the placenta. The lesions designated as Type 1 infarcts by Little (1960) probably result from recent circulatory stasis in the intervillous space. These lesions may be the source of the rise in serum lactic dehydrogenase (Little, 1959) and serum iso-citric dehydrogenase (Dawkins and Wigglesworth, 1960) in a few cases of normal labour and in most of the cases of labour in women with toxaemia. In addition, the placenta probably separates gradually during the latter part of labour. If placental function is impaired by toxaemia, the placental reserve may then be inadequate for the demands of labour and foetal death will result.

This series of 100 perinatal deaths due to asphyxia in labour was obtained over eleven years in a unit with a high standard of obstetric care and a special interest in the prevention of perinatal mortality. All perinatal deaths are reviewed monthly by obstetricians, paediatricians and pathologists. Obstetric management in specific problems is decided in the light of these reviews and is continually modified as the avoidable factors discussed in this paper are recognized. We feel that this approach is particularly valuable in the management of the

special problems of the many abnormal mothers delivered in this hospital. However, it appears that greater vigilance is necessary on two points:

(1) The timing of induction of labour in toxaemia.

(2) More frequent listening to the foetal heart during labour when any abnormality is present, perhaps with continuous recording of the foetal heart.

Summary

An analysis is presented of 100 foetal and neonatal deaths occurring as a result of asphyxia during labour.

Clinical associations and potentially avoidable factors are discussed.

The major causes of intra-partum asphyxia were thought to be complicated vaginal delivery, premature placental separation and inadequate placental reserve.

More than half the deaths occurred in association with maternal toxaemia. The combination of toxaemia with some other abnormality such as postmaturity or difficulties in labour, was especially hazardous.

Only 2 per cent of the deaths in this series had no discernible aetiological factor and postmaturity by itself seems to be a rare cause of foetal death during labour.

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EMBOLISM TO THE LUNGS BY TROPHOBLAST

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EMBOLISM to the lungs by trophoblast was first described by Schmorl in 1893. The illustration from his paper (Fig. 1) testifies to the accuracy of his observation. Schmorl's original description was based on an examination of the lungs of 17 eclamptic patients and 4 non-eclamptic patients. Since trophoblast was seen in the lungs of 14 of the 17 eclamptics, and in none of the 4 non-eclamptics, the emboli were at first thought to be of aetiological importance; further observations, however, particularly by Lubarsch (1893, 1899), Kassjanow (1896) and Schmorl himself (1905) showed that such embolism was not confined to women dying of eclampsia. Yet no investigation was made of the factors producing the embolism or of its significance.

Recently we have had the opportunity of examining histological material from 220 pregnant, parturient and puerperal women. This study deals with the incidence of trophoblastic embolism in this group, the factors that may have produced it and the effects of such embolism on the lungs. A comparison is also made between the incidence of trophoblastic embolism and the incidence of amniotic embolism. Part of this material has already been analyzed (Attwood, 1957; Park, 1957) while a more recent account of the phenomenon has been published by Bardawil and Toy (1959).

In vivo confirmation of the occurrence of pulmonary trophoblastic embolism, hitherto dependent on post-mortem studies, has recently been provided by Douglas and his colleagues (1959) who demonstrated particles of trophoblast in venous blood from the pregnant uterus. Their observations, however, did not allow them to draw any quantitative conclusions.

MATERIAL AND METHODS

Pulmonary tissue for microscopy from pregnant, parturient and puerperal women was collected from 3 centres:

30 cases from the Royal Infirmary, Dundee;
90 cases from the Royal Infirmary, Edinburgh;
100 cases from the Department of Pathology, Yale University School of Medicine.

In 120 of the cases, 8 semi-serial sections were examined from each block of tissue. In the other 100 cases, only one section was examined from each block. In many of the cases no more than one block was available so no attempt can be made to compare the incidence of trophoblastic embolism from lobe to lobe in the individual patient.

A quantitative measure of the amount of identifiable trophoblast was evolved to provide comparisons between individual patients and between groups of patients. This measure, the "trophoblastic index", is the number of particles of trophoblast seen in 1,000 sq. mm. of lung section. The validity of such an index depends on the accuracy of identification of intravascular particles as trophoblast. This is rarely difficult. The essential character of embolic trophoblast (see Figs. 2, 3, 4) is the possession of many virtually identical nuclei, closely packed and

usually coarsely granular, and a variable amount of cytoplasm. Though sometimes larger or smaller than the particles illustrated, they are always easily distinguished from other intravascular multinucleated bodies in the lungs, for example, clumped endothelium detached by artefact, emboli of bone marrow, close-packed lymphocytes or amniotic squames. In particular they can be readily differentiated from the embolic malignant trophoblast of chorion-carcinoma (Fig. 5). Confusion is also unlikely to arise with the irregularly shaped multi-lobulated and usually naked, pyknotic nuclei of the so-called pulmonary "megakaryocyte" (Figs. 6, 7). Pulmonary megakaryocytes were in fact found in every case though varying widely in frequency from cases to case. Moreover they were not confined to the lungs (see review by Sharnoff and Kim, 1958) and we have seen them quite frequently in the kidney.

Results

Trophoblastic emboli were found in 96 of the 220 cases, a frequency of 43·6 per cent which corresponds fairly closely to that of 52·3 per cent (57 of 109 cases) found by Bardawil and Toy (1959). Amniotic embolism was found in only 2 of the 220 cases. Bardawil and Toy also found 2 cases.

The true frequency of trophoblastic embolism is almost certainly higher than the figures given above for it has been our experience that the chances of finding trophoblast in the lung increase directly with the amount of tissue examined. When only one block of tissue was available 39·3 per cent of cases (57 of 145) showed trophoblast, whereas when more than 5 blocks were available the figure rose to 66·6 per cent (8 of 12 cases). Indeed, as was first maintained by Kassjanow (1896), it may well be that trophoblastic embolism occurs to some degree in every pregnancy.

In individual patients, however, the amount of trophoblast in the lung, the trophoblastic index, varies very greatly, and it does seem to be related to uterine activity. Thus there is an increase both in the frequency of trophoblastic embolism and in the height of the trophoblastic index with the approach and onset of labour

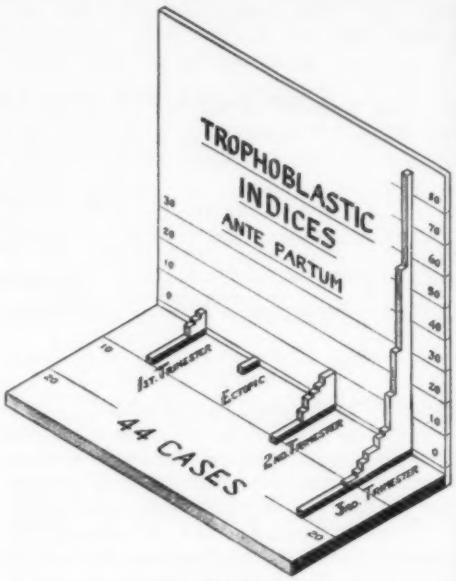

Fig. 8

An analysis of the 44 cases of ante-partum death. In each group the base-line indicates the number of patients; the blocks erected thereon indicate the number of patients within the group whose lungs contained trophoblast, as well as the height of their trophoblastic indices.
Note how both the proportion of "positive" cases, and the amount of trophoblast within the lungs, increase with the duration of pregnancy and the approach of parturition.

(Fig. 8) while the highest levels for both these measurements were reached in the group of patients who died either during labour or in the first 24 hours post-partum; not unexpectedly the two highest indices were found in cases of eclampsia in which irregular and excessive uterine contractions occur. The role of eclampsia as an especial promoter of pulmonary trophoblastic embolism has been analyzed, the 220 cases being divided, so far as was possible on the evidence of the clinical records, into 4 groups depending on the cause of death. Table I shows this subdivision with (*a*) the number of patients in each group, (*b*) the number within each group showing trophoblast in the lung, (*c*) their

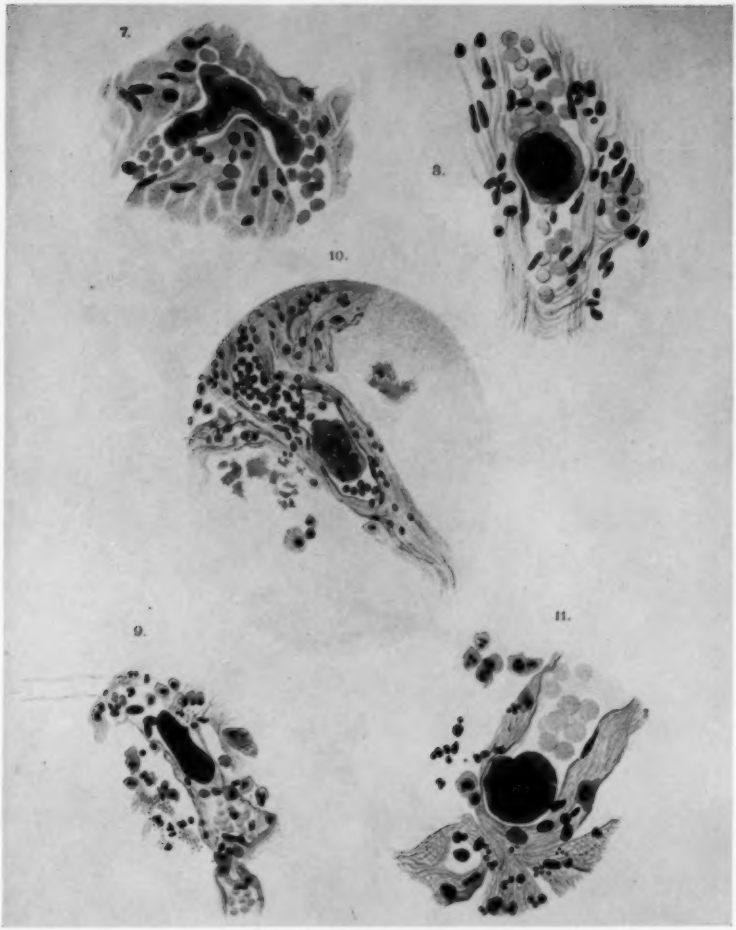

FIG. 1

A monochrome reproduction of Schmorl's original coloured illustration of trophoblastic emboli in pulmonary vessels. Photomicrographs of the fields from which these drawings were made appeared on the facing page in his monograph.

H.D.A., W.W.P. [612]

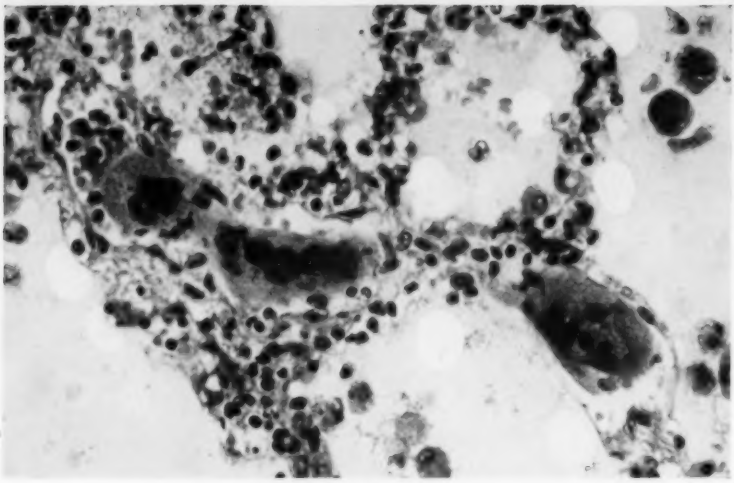

FIG. 2

Extensive blockage of a pulmonary capillary by a multinucleated mass of embolic trophoblast. H. & E. ×423.

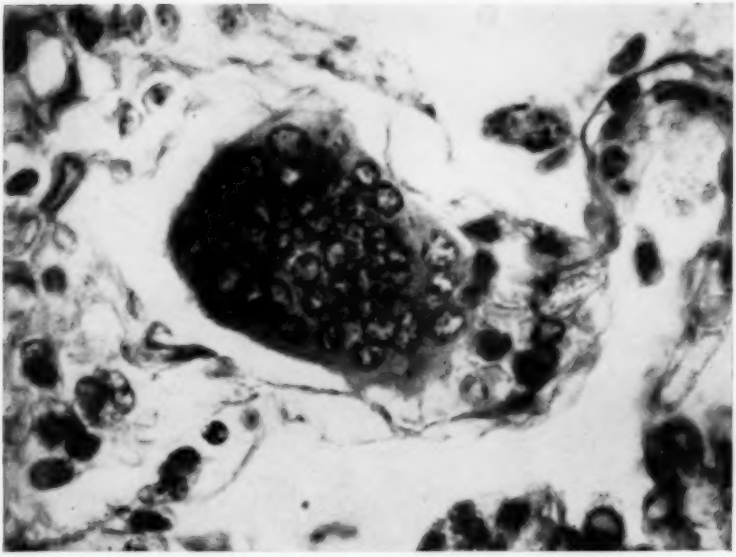

FIG. 3

A relatively large mass of syncytial trophoblast in a pulmonary capillary. Note the uniformity and close packing of the nuclei. H. & E. ×878.

H.D.A., W.W.P.

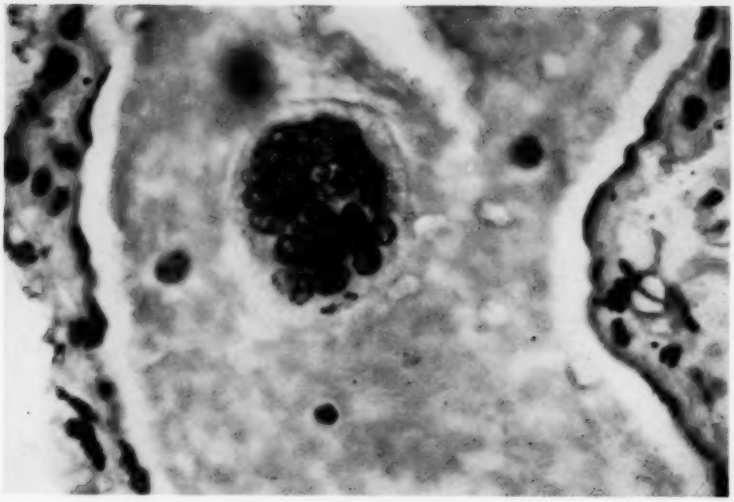

FIG. 4

Another syncytial mass. The nuclear appearances are characteristic. H. & E. ×878.

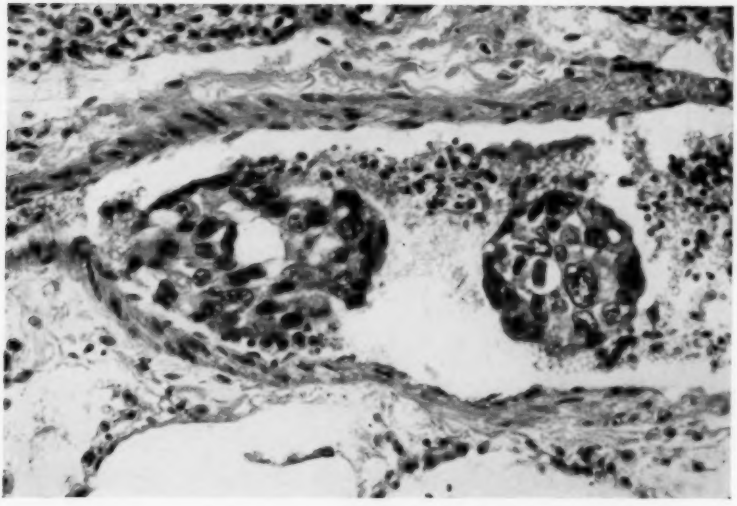

FIG. 5

Particles of embolic chorioncarcinoma in a pulmonary arteriole. In contrast to "normal" embolic trophoblast, these clumps of tissue are much larger and show prominent nuclear aberrancy and polymorphism. H. & E. ×450.

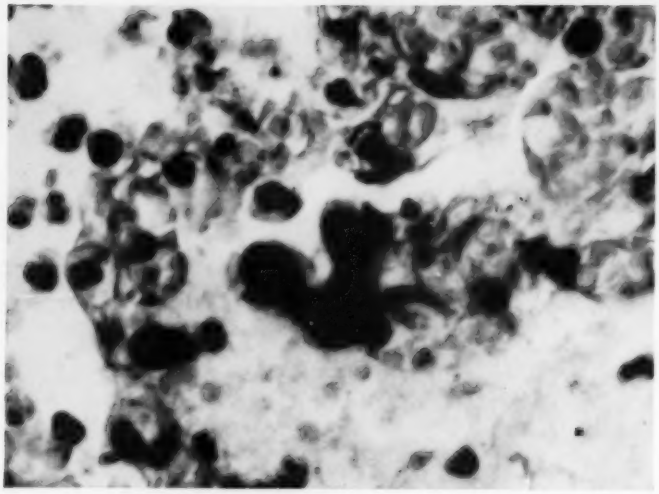

FIG. 6

A so-called pulmonary megakaryocyte. It appears as a solid mass of chromatin with a multilobular but not multinucleated structure. H. & E. ×945.

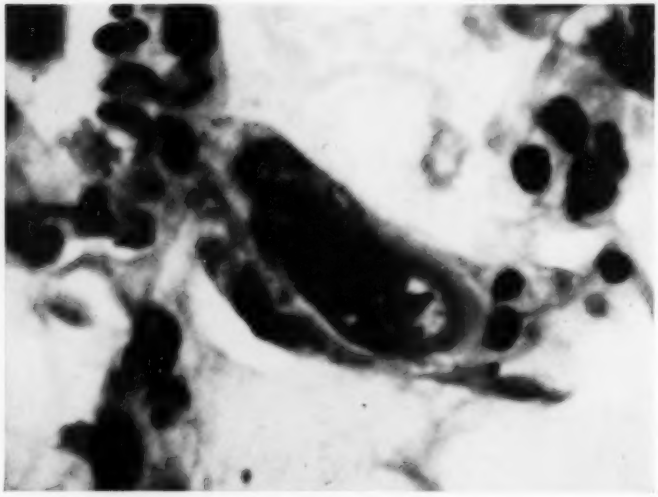

FIG. 7

Another pulmonary megakaryocyte. Preservation of internal nuclear structure, as is evident here, is not commonly seen. H. & E. ×1216.

H.D.A., W.W.P.

TABLE I

Shows the 220 Cases Divided into 4 Groups According to the Main Cause of Death, and, Within Each Group, the Number of Cases Showing Trophoblast Within the Lung and the Relevant Trophoblastic Indices

	Eclampsia and Pre-eclampsia	Haemorrhage and Shock	Sepsis	Other
Number of patients	33 (15% of total)	28 (13%)	63 (28%)	96 (43%)
Number with trophoblast in lungs	27 (81% of group)	12 (43%)	11 (17%)	46 (48%)
Trophoblastic indices	247, 87, 70, 70, 58, 50, 30, 20, 20, 20, 16, 15, 12, 10, 10, 10, 9, 8, 8, 8, 6, 5, 5, 4, 4, 2, 1	40, 35, 16, 16, 10, 10, 7, 6, 4, 4, 4, 4,	22, 22, 17, 13, 8, 5, 4, 3, 2, 2, 2	82, 81, 70, 56, 33, 32, 24, 20, 20, 20, 15, 13, 12, 11, 11, 10, 10, 9, 9, 8, 8, 7, 7, 7, 7, 6, 6, 6, 6, 5, 5, 5, 5, 5, 4, 4, 4, 4, 3, 2, 2, 2, 2, 2, 1, 1
Mean trophoblastic index ..	805÷33=24·4	156÷28=5·6	100÷63=1·6	662÷96=6·9

trophoblastic indices, and (*d*) the mean trophoblastic index for each group. It will be seen that the highest mean T.I. is found in the group of "eclampsia–pre-eclampsia". When this group is itself subdivided into those patients who had frank convulsions and the rest, as shown in Table II, it is found that the mean T.I. of the "convulsions" group is much the higher. These figures suggest strongly that it is the convulsions of eclampsia rather than the toxaemic disease *per se* that promotes the escape of trophoblast from the placenta. They show also that unusually large amounts of trophoblast can be displaced in patients dying from haemorrhage and shock, circumstances where uterine compression is likely to be performed during attempted haemostasis. Factors other than muscular contraction may well play a part. One of our cases, a patient who died during the performance of a difficult version, presumably with much disturbance of the placental site, showed no trophoblast within the lung; on the other hand, amongst the patients forming the group "other diseases" there are 4 with higher trophoblastic indices than any in the "haemorrhage and shock" group. In general it seems reasonable to conclude from the evidence contained in Figure 8 and in Tables I and II that the cause

TABLE II

Shows the 33 Cases in the Eclampsia–Pre-eclampsia Group Subdivided into "Convulsive" and "Non-convulsive" Subgroups, and the Relevant Trophoblastic Indices

	Convulsions	No Convulsions
Number of patients	16	17
Number with trophoblast in lungs	14	11
Trophoblastic indices	247, 87, 70, 58, 50, 20, 10, 8, 6, 5, 5, 4, 4, 2,	70, 30, 20, 20, 16, 15, 12, 10, 10, 9, 8
Mean trophoblastic index	576÷16=36	220÷17=13

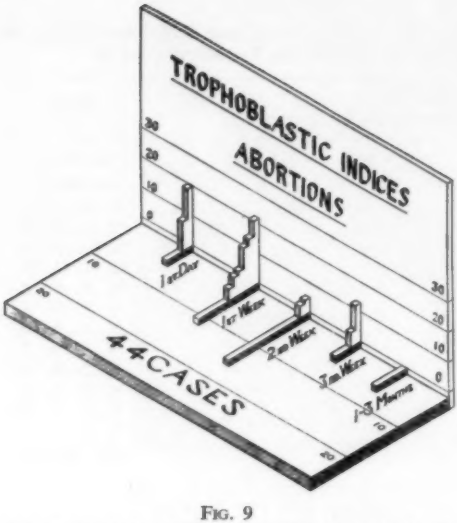

FIG. 9

A similar analysis of the 44 post-abortal deaths in the series. There is no evident correlation between the trophoblastic indices and the reported duration of the pregnancy, probably for the reasons mentioned in the text.

of trophoblastic displacement in "physiological" amounts during the course of pregnancy and normal labour is normal uterine contraction: that the main cause of trophoblastic escape in excessive amounts is undue "placental commotion" whatever the cause, whether it be prolonged labour, uterine manipulation or the excessive contractions of eclampsia: but that some other factor(s), possibly placental infarction with a loosening of trophoblastic attachment to the villi, may sometimes be a contributory cause.

The fairly close association of the total frequency of trophoblastic embolism and individual trophoblastic indices with increasing uterine activity, easily seen in Figure 8, is not so distinct in the 44 cases of abortion in the series (Fig. 9). This may be accounted for by the frequent inaccuracy of the clinical histories proffered, and by the variable length of time for which placental debris is retained within the uterus, in such cases.

Figure 10 shows that the proportion of patients whose lungs showed trophoblast was highest in those who died during delivery or the first week of the puerperium, 58 out of 100, and diminished rapidly thereafter. None was seen in the lungs of any patient who died after the 15th day of the puerperium. Closer analysis of the patients who died during the first week showed in fact that the greatest amounts of trophoblast were seen in those who died during the first 3 days after delivery, and particularly during the first 24 hours. It seems reasonable to conclude that the life of an embolic particle is ordinarily of about 3 days and only exceptionally exceeds 2 weeks.

No structural alteration in the pulmonary vasculature or parenchyma was seen that could be attributed to the trophoblastic emboli. A very occasional small vessel was, it is true, blocked

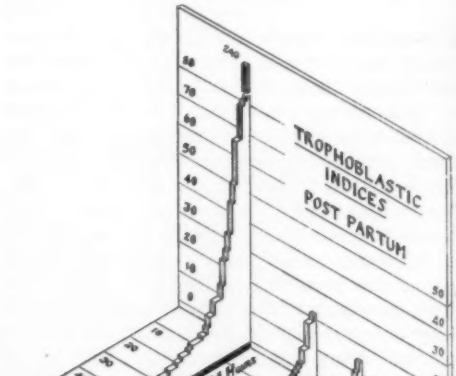

FIG. 10

This shows the distribution of the trophoblastic indices for those patients who died during or after labour. There is a rapid falling-off both in the proportion of "positive" cases, initially very high, and in the height of the indices, from the time of labour onwards.

by thrombus but we could not with assurance relate this to the presence of trophoblast within it. Shrinkage of the masses with increased pyknosis of nuclei can sometimes be seen, and this can be related to the number of days post-partum. It would seem that trophoblastic emboli gradually dissolve and leave no permanent structural alteration in the pulmonary vasculature. This hypothesis is certainly in keeping with the findings in a report of experimental trophoblastic embolism (Park, 1958).

Discussion

This quantitative investigation has shown that embolic trophoblast may be found in the lungs in very variable amount. There appears to be a broad association of the amount present in the lungs with the degree of uterine contraction. Thus, the amount appears gradually to increase with the duration of pregnancy and reaches its highest level during labour and the next 24 hours. In general the greatest quantities of trophoblast were found in the lungs of eclamptic patients who had had convulsions, whereas the quantities found in toxaemic patients who had not had convulsions were much less. This suggests that the escape of trophoblast in unusually large amount is caused by the convulsions rather than by the toxaemic aspect *per se* of the disease, and reinforces the view that uterine contraction or simple mechanical disturbance of the placenta is the main cause of trophoblastic dislodgement. It is worth recording that in no case in our series did we see a chorionic villus within the lung. Bardawil and Toy (1959), in their series of 109 cases, saw a single small villus within the lung from 2 of their patients; this, so far as we know, is the first occasion on which a villus has been seen in the lung in a non-molar pregnancy. These findings stand in sharp contrast to the statement, still recorded in current texts, that transportion of whole villi to the lungs occurs frequently if not invariably in every pregnancy. That villi may occasionally be carried to the lung during molar pregnancy, on the other hand, is well recognized.

Embolism of trophoblast has been identified as a cause of death in 4 cases (Hughes, 1930; Marcuse, 1954; Trotter and Tieche, 1956; Arnold and Bainborough, 1957). In 2 of these cases, those of Hughes and of Trotter and Tieche, the pregnancy was one of hydatidiform mole, with the mole still *in utero* at the time of death: in that of Marcuse an apparently normal pregnancy at the 6th month: and in that of Arnold and Bainborough, of uncertain origin but either a term pregnancy 3 years before death or an abortion 5 months before death. The amount of trophoblast in a hydatidiform mole may be so great, and its attachment to villi so tenuous, that escape to the lungs of a lethal amount is at least understandable. The reason for the escape of trophoblast in lethal volume in other circumstances is quite obscure, and the post-mortem evidence allowed neither Marcuse nor Arnold and Bainborough to offer an explanation. The highest trophoblastic index in our own series, one of 247, completely outwith the majority range, occurred in a patient with eclampsia. Interestingly enough, however, she died not from pulmonary obstruction but from a massive cerebral haemorrhage.

Whether, apart from the quite exceptional occurrence of lethal pulmonary vascular obstruction, the phenomenon of trophoblastic pulmonary embolism has any permanent or even temporary significance for the mother is still uncertain. There has recently been published by Wilcken, MacKenzie and Goodwin (1960) the account of a 32-year-old woman who, 6 months after a prolonged first labour, developed quite abruptly the signs and symptoms of pulmonary hypertension. A satisfactory therapeutic response to anticoagulant therapy led the authors to believe that the cause was "continuing small-vein thromboses with repeated minute pulmonary embolism"; since there was no history of overt venous thrombosis during the pregnancy or puerperium, the origin of the thrombi was presumed to be the pelvic veins. A therapeutically amenable pulmonary obstruction of this kind could conceivably have trophoblastic blockade as its basis with thrombotic "build-up" thereafter (and it is just possible that some such mechanism was concerned in Marcuse's case) but in view of our own observation, already mentioned, that no abnormal tissue reactions, intra- or extravascular, were present around the trophoblast

in any of the 220 cases, we think this unlikely. Nevertheless it is perhaps too soon to exonerate trophoblastic embolism, or even minimal amniotic fluid embolism, completely as a possible cause of later "idiopathic" pulmonary hypertension. The old problem whether or not there exists a specific syncytiolysin that rids the blood stream and lungs of embolic trophoblast is still unsettled. Only the isolation of such a substance from the circulating blood and demonstration of its selective action on fresh tissue or in tissue culture will settle the point.

Some of the problems in tissue immunity posed by the conceptus considered as a homograft have recently been outlined by Park (1959), and have been discussed also by Douglas and his co-workers (1959). It is now well known that tolerance to a homograft may be artificially induced by the injection of donor cell suspensions into immature animals, the "actively acquired tolerance" of Billingham, Brent and Medawar (1956). The view has been expressed by Douglas and his associates that a tolerance of this kind may be created in the human by the passage of trophoblast to the lungs: in their own words, "It is conceivable that . . . the migration of trophoblast into the blood stream throughout gestation is the means by which 'tolerance' is achieved." Now, when an immature animal is inoculated with a donor cell suspension, the animal is, as it were, being warned in advance of the nature of the graft that is to come. This cannot apply in pregnancy in the human. There is no way, so far as we can see, whereby the mother can be warned in advance of the nature of the tissues of the embryo with which she will be "grafted" during pregnancy. It would appear either that trophoblast is antigenically impotent or that there exists at the placental site some defensive antibody-neutralizing mechanism as yet undiscovered. The escape of trophoblast to the lungs might have some reinforcing effect upon such a defensive mechanism, though it may be doubted whether trophoblast within the pulmonary capillaries can do anything in this respect that cannot be done equally well or better in the placental blood lake. In contrast to Douglas and his colleagues, we ourselves rather suspect that embolism to the lungs by trophoblast is, immunologically speaking, irrelevant.

Summary

(1) Pulmonary tissue has been examined from 220 pregnant or puerperal women, and an analysis made both of the frequency with which trophoblast may be seen in the lungs, and, using a "Trophoblastic Index", of the amount of trophoblast in the lungs of individual patients.

(2) Trophoblast was seen in 43·6 per cent of the cases; but there are reasons for believing that the greater the amount of pulmonary tissue examined, the greater is the likelihood of finding trophoblast therein.

(3) The main cause of trophoblastic displacement appears to be uterine contraction and "placental commotion", however caused, though degenerative loosening of trophoblast from the villi may play a part.

(4) The greatest amounts of trophoblast were found in patients with eclampsia, a consequence almost certainly of the convulsions and undue contractions, not of the toxaemic element, of the disease. Relatively large amounts were also found occasionally in other circumstances.

(5) No chorionic villi were seen in the lungs in any case.

(6) No structural changes were seen in pulmonary tissues around trophoblastic emboli, nor did the emboli appear to predispose to the formation of thrombus.

(7) It seems doubtful whether trophoblastic pulmonary embolism has any significance in relation to homograft immunity mechanisms in pregnancy.

Acknowledgments

We wish to express our sincere thanks to Professor Margaret Fairlie, Dr. Averill Liebow and Dr. R. F. Ogilvie for access to the pathological material and clinical data used in this analysis: to Professor A. C. Lendrum for many helpful suggestions throughout: to Mr. J. Corkhill for much assistance with the photography; and to the Universities of St. Andrews and Edinburgh for permission to reproduce certain material originally incorporated in our respective Theses submitted in requirement of the regulations for the Doctorate of Medicine.

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A RADIOLOGICAL COMPARISON OF THE POSITIONS OF THE ANUS BEFORE AND AFTER DELIVERY IN 42 PRIMIGRAVID PATIENTS

BY

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THIS paper is concerned with an attempt to demonstrate radiologically changes in the position of the anus before and after the first delivery and to correlate them with trauma at delivery. It concerns 42 primigravid women, unselected except in so far as an X-ray was deemed necessary at the 38th week of gestation.

Young (1951) stated that, as a result of pelvic floor relaxation, the anus is displaced downwards and backwards. He gave the following average measurements for the distance between the lower margin of the symphysis pubis and the centre of the anal opening: nulliparae, 2·6 inches (6·6 cm.); parous patients without prolapse, 2·9 inches (7·3 cm.); patients with prolapse, 3·4 inches (8·6 cm.).

By means of levator myography Berglas and Rubin (1953) and Muir (1955) demonstrated that the levator plate, the portion of the levator lying behind the rectum, is horizontal in nulliparae but slopes downward and forward from the coccyx in cases of pelvic floor relaxation and as a result the anus is displaced down and back.

METHOD

A mushroom-shaped obturator with a metal core was inserted into the anal canal with the flat part strapped firmly to the anal margin. The lateral X-ray in the 38-weeks pelvimetry was taken with the obturator in place and a similar X-ray taken with the obturator again in place at the 6-weeks postnatal examination. Figure 1 shows these two X-rays superimposed, D_1 being the anal position ante-partum and D_2 post-partum. The beam was centred on the ischial spines and Figure 2 shows the apparent differences in the antero-posterior diameter of the bony pelvis in the films before and after delivery measured between the upper border

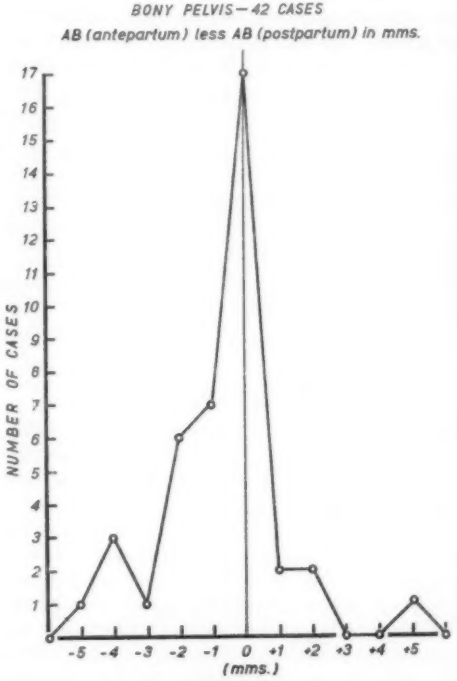

FIG. 2

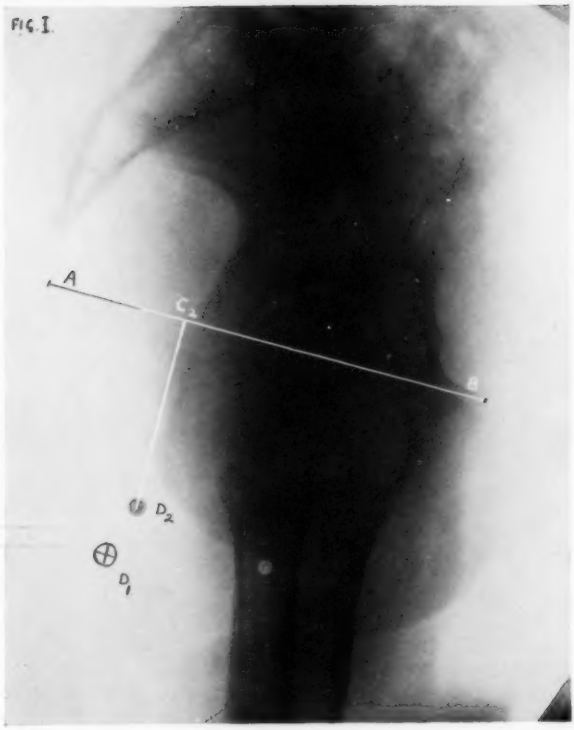

FIG. 1

of the symphysis pubis and the lower extremity of the sacrum. These two points were selected because they were easily identified in all films and the line joining them is roughly parallel to the pubo-coccygeus muscle. In each case the measurement after delivery was deducted from that before delivery and the resulting number plotted horizontally while the number of cases was plotted vertically.

Figure 2 shows that in 17 cases (40 per cent) the apparent size of the pelvis was unchanged, in 13 cases (31 per cent) the apparent increase was one to two millimetres, while in 7 cases (17 per cent) the increase was more than two millimetres. In 4 cases (10 per cent) the apparent decrease was one to two millimetres while in one case (2 per cent) the decrease was more than two millimetres; in this case the diagnosis was "contracted pelvis" and the head was deeply engaged at the time of the X-ray examination making it possible that the head was expanding the pelvis. It will be seen that in 81 per cent of the cases the difference was two millimetres or less and in the great majority the pelvis appears to have increased in size or remained unchanged.

The superior margin of the symphysis was joined to the lower extremity of the sacrum in Figure 1 and a perpendicular dropped to the anus. Figure 3 is obtained by dividing the length

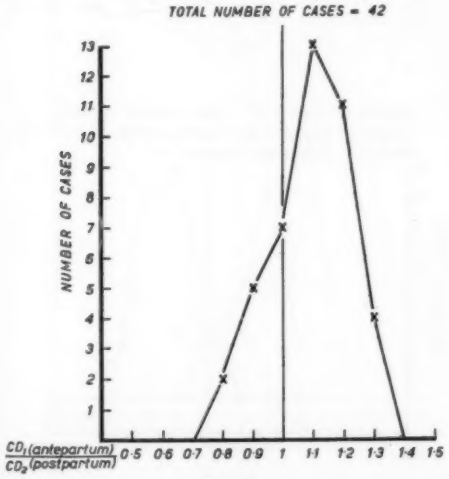

FIG. 3

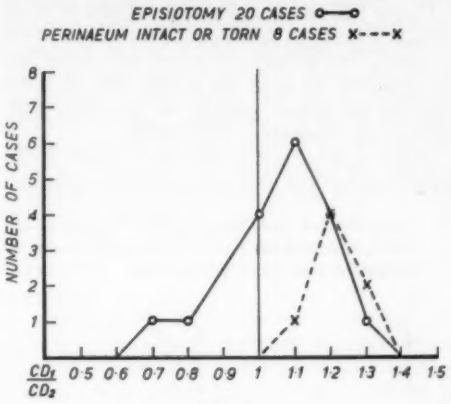

FIG. 4

of this perpendicular before delivery by that after delivery and plotting the resulting number horizontally against the number of cases vertically. In the majority of cases the number is greater than unity showing that the anus lies at a higher level post-partum than ante-partum.

Figure 4 shows curves for spontaneous delivery in which an episiotomy was done (20 cases) and those in which the perineum was intact or torn at delivery (8 cases). It will be seen that the curve for intact perineums and tears lies to the right of that for episiotomies showing a greater elevation of the anus post-partum in the former.

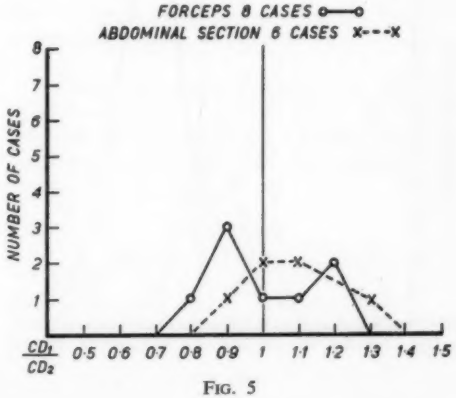

FIG. 5

Figure 5 shows a similar comparison between forceps delivery (8 cases) and abdominal section (5 cases). The forceps curve has two peaks but the majority of cases lie to the left of unity showing an actual sagging of the anus after delivery as compared with before.

Figure 6 shows curves for infants with birth-weights under and over seven pounds, excluding cases of abdominal section. As one might expect there is a greater post-partum elevation of the anus in those patients who had smaller babies.

Figure 7 shows curves for Chinese and European mothers. It would appear that the elevation is greater in the Chinese but this can result from the difference in average ages of the two groups, 23 years in the Chinese and 31 years in the Europeans. The distribution according to age is shown in Figure 8, greater elevation occurring in the younger group.

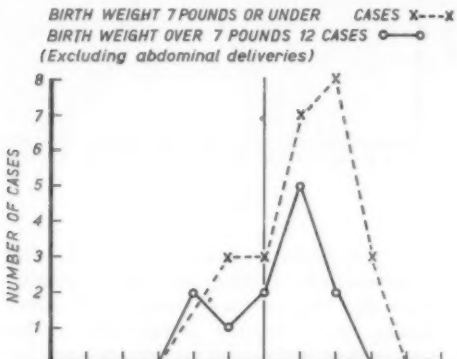
BIRTH WEIGHT 7 POUNDS OR UNDER CASES X---X
BIRTH WEIGHT OVER 7 POUNDS 12 CASES O—O
(Excluding abdominal deliveries)
NUMBER OF CASES
CD1/CD2
0·5 0·6 0·7 0·8 0·9 1 1·1 1·2 1·3 1·4 1·5

FIG. 6

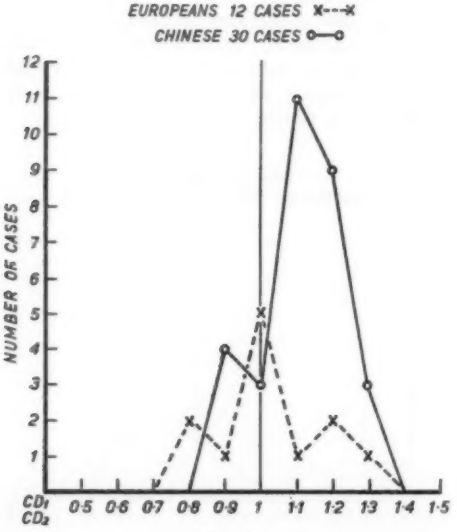

FIG. 7

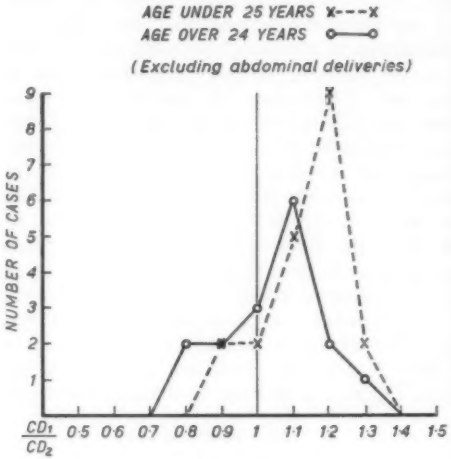
AGE UNDER 25 YEARS X---X
AGE OVER 24 YEARS O—O
(Excluding abdominal deliveries)
NUMBER OF CASES
CD1/CD2
0·5 0·6 0·7 0·8 0·9 1 1·1 1·2 1·3 1·4 1·5

FIG. 8

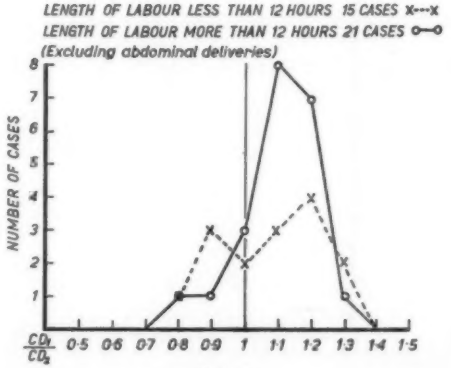
LENGTH OF LABOUR LESS THAN 12 HOURS 15 CASES X---X
LENGTH OF LABOUR MORE THAN 12 HOURS 21 CASES O—O
(Excluding abdominal deliveries)
NUMBER OF CASES
CD1/CD2
0·5 0·6 0·7 0·8 0·9 1 1·1 1·2 1·3 1·4 1·5

FIG. 9

Figure 9 shows curves for patients with labours lasting less than 12 hours and longer than this period. No difference in tendency is noted. Finally Figure 10 gives a curve for patients in whom the presenting part was within one centimetre of the level of the ischial spines at the antenatal examination or lower, that is, roughly, those cases in whom the head was engaged compared with the general curve. It can be seen that the shapes of these curves approximate closely to each other, suggesting that there is no greater sagging of the anus when the head is engaged as compared with cases in whom the head is free.

Discussion

The present investigation is an attempt to ascertain by a simple, generally applicable means what changes take place in the position of the anus following the first delivery and to correlate various factors with these changes. The number of cases in this series is too small to draw definite conclusions but it is of interest to note the expected departure from the average when abdominal section is compared with forceps delivery, small babies with larger babies, young mothers with older mothers. The unexpected exception is the better apparent recovery in patients who had intact or torn perineums as compared with those who had episiotomies performed. The average age of the episiotomy patients was 24 years against 21 years for those who had intact or torn perineums. The average weight of the babies in the former was 6 pounds 13 ounces against 6 pounds 8 ounces in the latter. These two factors may explain the apparently inferior results when episiotomy was done.

Originally my intention was to employ this technique on a large number of cases in the hope of being able to assess pelvic floor damage incident to a variety of types and methods of delivery as it is felt that women suffer much disability and disfigurement from childbirth which is overlooked; it never appears in reports and numerical computation is difficult. However, this preliminary study suggests that the method is not sensitive enough to warrant continuing with it.

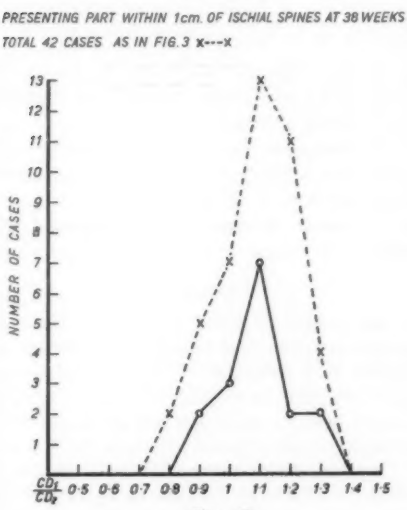

FIG. 10

Summary

By inserting a metallic obturator in the anal canal a record of the position of the anus in relation to the bony pelvis was obtained at 38-weeks gestation and at 6-weeks post-partum in 42 primigravid patients. The antero-posterior diameter of the bony pelvis appeared to remain unchanged or to be slightly enlarged in most cases after delivery. Different degrees of elevation of the anus after delivery were found in contrasting groups of patients.

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TOXAEMIA AND PRE-PREGNANCY WEIGHT

BY

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IT is well recognized that pre-eclamptic toxaemia is often associated with excessive gain in weight during pregnancy. Recently it has been suggested that the chance of developing toxaemia is related to pre-pregnancy body build, being greater than average in obese women and less than average in thin women (Stewart and Hewitt, 1960).

This, if true, is an important observation but for a number of reasons it is not an easy one to confirm or refute. The most serious obstacle in the approach to the problem is the difficulty of recording accurately the immediate pre-pregnancy weight of a sufficiently large number of women. Weights taken during pregnancy are of little use since they are influenced by an excessive gain in some cases of toxaemia and by varying durations of gestation. Weights taken after delivery are suspect, for an excessive gain during pregnancy may result in a permanent change in physique. There remains the possibility of asking women during pregnancy or after delivery what their weight was before they became pregnant. Information collected in this manner is open to the objection that memory can be faulty or answers biassed. For obvious reasons, however, this is the only method by which a large series of pre-pregnancy weights can be accumulated, and it must be explored.

In a survey concerned with the effect of maternal smoking habits upon the birth weight of children (Lowe, 1959), recently-delivered women were questioned about their weight immediately before pregnancy. Since information was also collected about the complications of pregnancy experienced by the women, it has been possible to examine this material for evidence of a relation between pre-pregnancy physique and toxaemia.

MATERIAL

The data relate to 2,042 consecutive deliveries (single births only), in six Birmingham maternity hospitals during 1958. Although the enquiry was primarily concerned with birth weight and smoking habits, any mention in the hospital records of toxaemia, pre-eclamptic toxaemia, albuminuria or a diastolic pressure of 90 mm. Hg or over was noted. For 174 women data about age, parity, height or remembered pre-pregnancy weight were missing. The analysis which follows is concerned with 1,868 women for whom all information was complete. They were divided into four groups:

(1) Women with Toxaemia: 89 who were noted in the hospital records to have had toxaemia, pre-eclamptic toxaemia or a diastolic pressure of 90 or over and albuminuria.

(2) Women with Albuminuria: 56 who were noted to have had albuminuria without mention of raised blood pressure.

(3) Women with Raised Blood Pressure: 111 who had had a diastolic pressure of 90 or over without mention of albuminuria.

(4) All Other Women: the remaining 1,612 women.

RESULTS

In this sample of 1,868 women delivered in Birmingham hospitals the incidence of toxaemia, as defined and recorded in the hospital notes, was 4·8 per cent. In addition a further 3·0 per cent were said to have had albuminuria, with no mention of raised blood pressure, and 5·9 per cent raised blood pressure with no mention of albuminuria (Table I). The percentage incidence of toxaemia and of the two related conditions was higher for primiparae than multiparae.

TABLE I

Percentage Incidence of Toxaemia and Related Conditions

	Primiparae		Multiparae		Total	
Women with toxaemia	5·5	(60)	3·7	(29)	4·8	(89)
Women with albuminuria	3·6	(40)	2·1	(16)	3·0	(56)
Women with raised blood pressure	6·4	(70)	5·3	(41)	5·9	(111)
All other women	84·5	(926)	88·8	(686)	86·3	(1,612)
Total	100	(1,096)	100	(772)	100	(1,868)

The incidence of toxaemia for the combined data (all parities) used by Stewart and Hewitt (1960) was 14·5 per cent. This is much higher than the incidence of toxaemia in the Birmingham sample (4·8 per cent), and a little higher than toxaemia, albuminuria and raised blood pressure combined (13·7 per cent). It is proposed, therefore, to begin by exploring the association between pre-pregnancy physique and the incidence of toxaemia and related conditions combined (15·5 per cent for primiparae and 11·1 per cent for multiparae) before examining the sub-groups separately.

From Table II and Figure 1 it appears that for first pregnancies there was a striking and consistent relationship between pre-pregnancy weight and the recorded incidence of what will here be called toxaemic conditions. The incidence increased regularly from 11·1 per cent for women who stated that they had weighed less than 110 pounds before conception to twice that figure (22·7 per cent) for women who had weighed 150 pounds or more. The trend for multiparae although less consistent (the numbers were smaller and the group less homogeneous) was equally striking, showing a threefold

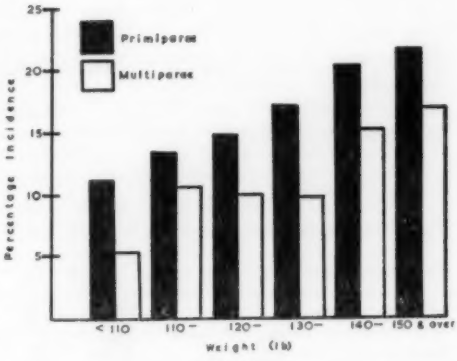

FIG. 1

Incidence of toxaemic conditions related to pre-pregnancy weight.

TABLE II

Percentage Incidence of Toxaemic Conditions Related to Pre-pregnancy Weight

Parity	Weight (pounds)						Total
	<110	110–	120–	130–	140–	150–	
Primiparae ..	11·1 (189)	13·4 (298)	14·9 (208)	17·2 (186)	20·5 (127)	22·7 (88)	15·5(1,096)
Multiparae ..	5·2 (116)	10·7 (177)	10·0 (130)	9·8 (133)	15·2 (99)	17·1 (117)	11·1 (772)

TABLE III

Percentage Incidence of Toxaemic Conditions Related to Height

Parity	Height (inches)					Total
	<62	62–	63–	64–	65–	
Primiparae ..	14·3 (251)	13·0 (184)	18·3 (175)	15·2 (204)	16·7 (282)	15·5 (1,096)
Multiparae ..	11·3 (195)	7·2 (125)	12·1 (116)	13·0 (108)	11·8 (228)	11·1 (772)

TABLE IV

Percentage Incidence of Toxaemic Conditions Related to Body Build

Parity	Height (inches)/$3\sqrt{\text{Weight (pounds)}}$					Total
	<11·5	11·5–	12·0–	12·5–	13·0–	
Primiparae ..	27·8 (18)	18·6 (70)	18·0 (239)	13·6 (420)	14·9 (249)	15·5 (1,096)
Multiparae ..	21·9 (32)	13·2 (76)	15·4 (182)	9·2 (273)	7·7 (209)	11·1 (772)

TABLE V

Percentage Incidence of Toxaemia and Other Conditions in Primiparae Related to Body Build

	Height (inches)/$3\sqrt{\text{Weight (pounds)}}$			Total
	<12·5	12·5–	13·0–	
Women with toxaemia	4·3 (14)	5·7 (24)	6·3 (22)	5·5 (60)
Women with albuminuria	4·6 (15)	2·1 (9)	4·6 (16)	3·6 (40)
Women with raised blood pressure ..	9·8 (32)	5·7 (24)	4·0 (14)	6·4 (70)
All other women	81·3 (226)	86·4 (363)	85·1 (297)	84·5 (926)
Total	100 (327)	100 (420)	100 (349)	100 (1,096)

TABLE VI

Percentage Incidence of Raised Blood Pressure in Primiparae Related to Age and to Body Build

Age (years)	Height (inches)/$3\sqrt{\text{Weight (pounds)}}$			Total
	<12·5	12·5–	13·0–	
<25	7·3 (178)	4·8 (270)	4·1 (244)	5·2 (692)
25–29	12·4 (89)	7·8 (103)	3·8 (78)	8·1 (270)
30–	13·6 (59)	6·3 (48)	3·7 (27)	9·0 (134)
Total	9·8 (326)	5·7 (421)	4·0 (349)	6·4(1,096)

increase (from 5·2 per cent to 17·1 per cent) over the same range.

Weight and stature are closely related. The next step therefore is to examine the occurrence of toxaemia conditions in relation to maternal height. This is done in Table III and there is perhaps a suggestion that the incidence may have been a little higher among the taller women, but the relationship is uncertain, irregular and not at all comparable with the weight relationship.

To define obesity with any accuracy, multiple measurements (including measurement of subcutaneous fat) are called for. Unfortunately from the Birmingham enquiry only weight and height were available. However, if a single index of body build has to be chosen, $Ht/3\sqrt{wt}$ is possibly the least objectionable, and has been used in Table IV and Figure 2. As might be expected in view of the findings with regard to weight and height, the incidence of toxaemic conditions in both primiparae and multiparae was closely related to this index of body build. Since thin women have high indices and obese women low indices, the relationship was, of course, an inverse one. (A woman with a height of 66 inches and weight of 200 pounds has an index of 11·3: a woman of the same height, but weighing only 100 pounds has an index of 13·6.) For primiparae there was a twofold increase in incidence (from 14·9 per cent to 27·8 per cent) and for multiparae a three-fold increase (from 7·7 per cent to 21·9 per cent) from the thin to the obese end of the scale.

So far patients stated in hospital records to have had toxaemia or pre-eclamptic toxaemia have been grouped under the general heading of toxaemia conditions with those for whom toxaemia was not specifically mentioned but who were recorded as having had albuminuria or a raised blood pressure (diastolic pressure of 90 mm. or higher). The three sub-groups must now be considered separately. For this purpose only data relating to primiparae are examined. (The number of multiparae was small; they formed a very heterogeneous group with parities ranging from 2 to 9; many had been admitted for complications of pregnancy or labour; and, most important, their pre-pregnancy weight may possibly have been influenced by toxaemia in earlier pregnancies.) The results are a little unexpected (Table V and Fig. 3). It appears that the relation between the combined group of toxaemic conditions and pre-pregnancy body build was entirely due to those patients who were reported to have had a raised blood pressure without mention of albuminuria or toxaemia. Albuminuria by itself

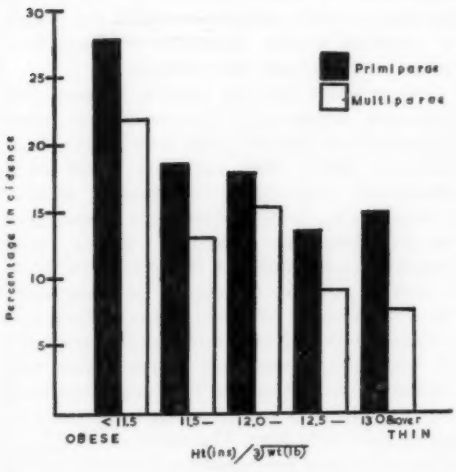

FIG. 2

Incidence of toxaemic conditions related to body build.

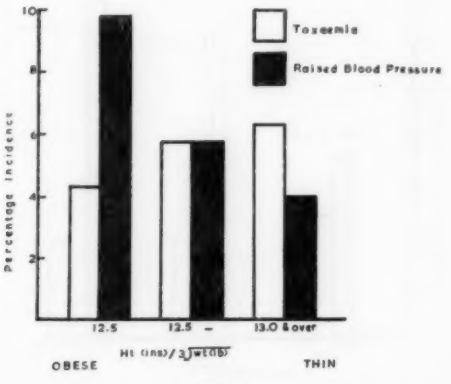

FIG. 3

Toxaemia and raised blood pressure in primiparae related to body build.

appeared to be unrelated to the index of body build, while specified toxaemia showed, if anything, a slight trend in the reverse direction (i.e., was inversely related to pre-pregnancy obesity). This inverse relationship was probably a chance phenomenon, for the numbers were very small ($\chi^2=1{\cdot}41$; n=2; $p>0{\cdot}3$). But there can be no doubt about the significance of the relationship between raised blood pressure and the index ($\chi^2=9{\cdot}90$; n=2; $p<0{\cdot}01$).

Weight increases with age. It is possible, therefore, that the higher incidence of raised blood pressure among obese women may be no more than the reflection of a relationship between raised blood pressure and age. From Table VI and Figure 4, which relate raised blood pressure both to the body-build index and to age, it is clear that this was not so. The proportion of women reported to have had a raised blood pressure did in fact increase with age (from 5·2 per cent under 25 years to 9·0 per cent at 30 years and over). But for each of the three age groups there was still a striking relationship between blood pressure and obesity.

Discussion

From an examination of data collected in two surveys designed for other purposes Stewart and Hewitt (1960) concluded that the incidence

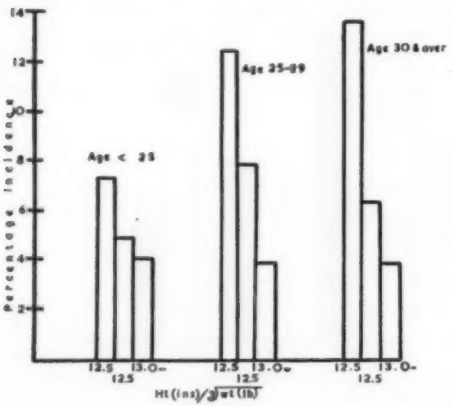

Fig. 4

Raised blood pressure in primiparae related to body build.

of toxaemia was higher than average among women who before pregnancy were overweight for their height and lower among those who were underweight for their height. At first sight the data relating to 1,868 women delivered in Birmingham hospitals appear to support this conclusion. Closer inspection of the material, however, reveals that the demonstrated relation between pre-pregnancy body build and the group of toxaemic conditions as defined is entirely due, at least in so far as primiparae are concerned, to the inclusion within this group of women reported in the hospital notes to have had a diastolic pressure of 90 mm. or higher without specific mention of either toxaemia, pre-eclamptic toxaemia or albuminuria.

It is generally agreed that blood pressure is related to age and to weight but not to height (Symonds, 1923; Robinson and Brucer, 1939; Gover, 1948; Bøe, Humerfelt and Wedervang, 1957). It has also been shown that, independently of the underlying arterial pressure, sphygmomanometer readings are directly related to arm circumference (Ragan and Bordley, 1941). In these respects the women reported to have had raised blood pressure without mention of toxaemia behaved as would be expected if they were an arbitrarily chosen section of the normal distribution of blood pressure in the general population—their proportion within the sample of pregnant women increased with age and, independently of age, with obesity.

This suggests that the relation between pre-pregnancy weight and "toxaemia" uncovered by Stewart and Hewitt (1960) may be due to the inclusion within their toxaemia group of a substantial proportion of women without toxaemia who, because they were obese, gave sphygmomanometer readings at a level commonly associated with that condition. There is internal evidence to support this suggestion. The incidence of toxaemia among primiparae in their sample of Northamptonshire women was 18·4 per cent; among their Surrey women with premature births it was 30·2 per cent and among the controls 16·8 per cent. These proportions are exceptionally high. The combined incidence of toxaemia and pre-eclamptic toxaemia among primiparae in the general population is uncertain (largely because these conditions are by

no means clearly defined clinical entities), but it is certainly less than 10 per cent and probably somewhere in the region of 5 per cent (Ministry of Health, 1949; Dieckmann, 1952; Gemmell, Logan and Benjamin, 1954; College of General Practitioners, 1957). The corresponding incidence in the Birmingham series was 5·5 per cent.

In conclusion it must be admitted that both the Birmingham data and the data used by Stewart and Hewitt are open to criticism on two grounds: they were derived from surveys designed for purposes unrelated to the problem of toxaemia and pre-pregnancy weight; and the incidence of toxaemia was estimated in retrospect from hospital records. Whether or not women who are overweight for their height are more likely than those who are underweight to develop toxaemia during their first pregnancy must therefore remain an open question.

Summary

It has been suggested that women who are overweight for their height may be more liable to develop toxaemia during pregnancy than those who are underweight. The hospital records of 2,042 women who shortly after delivery had been questioned about their pre-pregnancy weight were examined from this point of view.

There was no significant relation between recorded toxaemia or pre-eclamptic toxaemia and body build. But the proportion of women stated to have had a diastolic pressure of 90 mm. or higher was clearly related to obesity.

Since blood pressure in the general population is directly related to weight, it is thought that this may have confused the issue in the earlier report.

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CHLORPROMAZINE JAUNDICE IN PREGNANCY

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JAUNDICE is a recognized complication of chlorpromazine administration. Many cases have been recorded and 10 cases occurring in pregnant women are included in these reports (Bensohn and Wallace, 1955; Kreps, 1955; Kelsey *et al.*, 1955; Elliott, 1955; Kinross-Wright and Moyer, 1956; Shay and Siplet, 1957; Graham, 1957; Gebhart *et al.*, 1958). We should like to record a case of jaundice following the use of chlorpromazine for hyperemesis gravidarum.

CASE REPORT

The patient, Mrs. E.W., aged 42 years, attended the hospital antenatal clinic on 31st July, 1959. She had then reached the 12th week of her 5th pregnancy. Her doctor's letter stated that there had been severe hyperemesis but that improvement had followed the prescription of chlorpromazine, 25 mg. thrice daily for about 14 days. The patient's condition was considered to merit in-patient supervision and admission was arranged for the following day.

The only important past illness was a "nervous breakdown" lasting several months and accompanied by marked loss of weight. This occurred in 1957. Treatment was given at home; chlorpromazine was not used; recovery was complete. There was no past history of jaundice.

Her four previous pregnancies were uncomplicated and ended in spontaneous deliveries of healthy infants. The last confinement took place in this hospital in 1948.

On admission the patient gave a history of severe vomiting beginning soon after the first missed menstrual period. The vomiting had occurred after food and between meals. No solid food had been retained for five days. Her weight had fallen from 140 to 126 pounds. Her urinary output had diminished and her bowels had not acted for 4 days. Hiccough was present. There had been no abdominal pain, no shivering attacks and no pyrexia. The patient was seen to have a mild icterus but there was no serious dehydration. Her temperature and pulse-rate were normal. Her blood pressure was 120/80 mm. Hg. No abnormality was detected on examination of her heart and lungs. On abdominal examination her uterus could be felt to extend 2 finger-breadths above the symphysis pubis. No enlargement of liver or spleen and no abdominal tenderness were elicited. Her urine contained bile salts, bilirubin and urobilinogen, but was free from albumin, acetone and sugar. Her serum bilirubin was 2·5 mg. per cent. Her blood was Rh positive, group "A" and the Kahn test was negative. Her haemoglobin was 12·6 g./100 ml. A diagnosis of hyperemesis gravidarum with chlorpromazine jaundice was made. The patient was not ill enough to be jaundiced as a direct sequel to her hyperemesis. Malignant extra-hepatic biliary obstruction was considered to be unlikely in view of the history and findings, and the later course of the illness confirmed this opinion. The presence of a "silent" calculus in the extra-hepatic biliary

Date	4th August, 1959	12th August, 1959	21st August, 1959	17th September, 1959	23rd September, 1959	24th September, 1959	25th September, 1959	26th September, 1959	27th September, 1959	28th September, 1959	8th October, 1959	27th October, 1959	10th November, 1959	30th November, 1959	9th December, 1959	16th December, 1959	30th December, 1959	6th January, 1960	12th January, 1960	18th January, 1960	9th February, 1960	14th February, 1960	9th March, 1960	4th May, 1960
Week of pregnancy			14					20			22		26	29			34							
Thymol turbidity (units)*	1	1	1	1								1	1	1	1		1	1	2	2	2		2	2
Serum bilirubin (mg. per 100 ml.)	3·8	7·1	5·2	7·8	5·2	5·8	6·0	6·4	6·4	4·8	5·0	3·8	4·0	3·7	3·6		4·8	3·2	4·5	3·6	1·2		1·6	1·3
Serum alkaline phosphatase (King-Armstrong units per 100 ml.)	37	43	59	21								36	55	63	46		62	46	90	92	98		50	51
Serum cholesterol (mg. per 100 ml.)													300						270		580		480	320
Serum albumin (g. per 100 ml.)	4·0	4·0	3·8	3·3								4·2	4·0	4·1	4·1		3·9	2·7	2·9	3·6	4·2		3·9	4·0
Serum globulin (g. per 100 ml.)	3·4	3·2	3·1	3·2								3·6	3·7	2·9	2·8		3·0	3·4	3·0	3·7	3·1		3·7	3·2
Serum G.O.T. (Sigma Fraenkel units)		96	58	35								24	38	32	50		50	34	34	40	68		38	40
Serum G.P.T. (Sigma Fraenkel units)		74	50	25								20	19	20	22		22	16	19	22	52		22	32
Zinc sulphate turbidity (units)†	2	2	2	2								1	2	1	4		2	2	2	3			3	3
Ammonium sulphate turbidity (units)†	3	3	5	4								4	4	5	5		4	3	3	4			3	2
Red blood corpuscles (millions/cu.mm.)							3·5									3·4								
Haemoglobin (per cent)‡		57					68									66						80		
Colour index							0·98									0·96								
White blood corpuscles (thousands/cu.mm.)							6									6·2								
Polymorphs (per cent)							72									61								
Lymphocytes (per cent)							22									32								
Large mononuclears (per cent)							5									5								
Eosinophils (per cent)							1									2								

* Maclagan † Kankel ‡ 100% = 14·6 g./100 ml.

tract was thought to be a remote possibility. The initial treatment consisted of a diet of milk, glucose and other fluids, sodium phenobarbitone gr. 3 intramuscularly 8-hourly and vitamin B_1 intramuscularly twice daily.

By 3rd August the jaundice had increased. Intravenous glucose 10 per cent followed by 5 per cent was given with benefit. The results of liver function tests and other laboratory findings at this time and later are given in Table I; electrophoretograms are given in Figures 1 and 2. The patient's sickness ceased and her appetite improved, and she was discharged home on 16th August to continue supervision at the antenatal clinic. She was seen there on 21st August and 4th September. At first she felt better, having a little nausea but no vomiting. The size of her uterus corresponded to the duration of amenorrhoea; her urine was free from albumin; her blood pressure was normal and her weight 126 pounds. Soon, however, she developed a generalized pruritus which persisted for many weeks and for which antihistaminics, local applications and sedatives were tried without lasting benefit. A sudden increase in her jaundice with lethargy and depression occurred. Re-admission to hospital took place on 16th September. There was no vomiting and no pain and her appetite for a low-fat diet was satisfactory. Skin irritation was troublesome and bleeding per rectum followed defaecation. Her stools were pale and her urine dark. Foetal movements were felt. Her blood pressure was 115/65 mm. Hg and her pulse rate 64 per minute. Examination of her heart and lungs revealed no abnormality. Her uterus was the size of a 22-weeks pregnancy after 19-weeks amenorrhoea. The liver was not enlarged and there was no abdominal tenderness. Rectal examination revealed moderately severe haemorrhoids. There was no bleeding at the time of the examination; no neoplasm was felt. The clinical impression was still that the jaundice was due to chlorpromazine.

In accordance with Graham's recommendations (1957) an expectant policy was adopted. Excretion cholecystography was attempted but the biliary tract failed to outline. The patient's weight on 22nd September was 123 pounds; it showed slight fluctuations with a maximum

FIG. 1

Electrophoretic pattern of serum proteins on 10th November, 1959, showing a prominent β-globulin peak seven weeks before the onset of proteinuria.

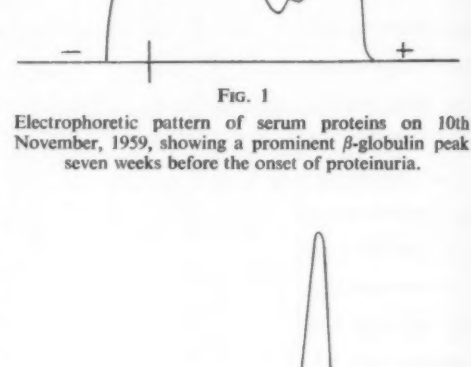

FIG. 2

(*a*) Electrophoretic pattern of serum proteins on 30th December, 1959, showing a further increase in the β-globulin fraction.

(*b*) Electrophoretic pattern of dialysed urine on 30th December, 1959, showing protein fractions corresponding to albumin, β- and γ-globulins. Total urinary protein = 0·7 g./100 ml.

of 128 pounds and a fall to 121 pounds before delivery. On 28th September A.C.T.H. gel was prescribed, 50 units twice daily for 4 days. A slight clinical improvement followed this, but the patient's condition was, in any case, subject to fluctuations. At times the jaundice was deeper and there was concomitant marked fatigue, nausea and vomiting. At other times, though the jaundice was obvious, the patient's condition gave no cause for anxiety and justified the conclusion that it was not due to a malignant growth. On 8th October a trial of prednisone was begun in a dose of 2·5 mg. twice daily. This was increased to 5 mg. twice daily on 10th October. Her illness continued to present the picture of obstructive jaundice with the fluctuations recorded. During the time that prednisone was used the level of the serum bilirubin showed a slight fall.

By 9th November the uterus was the size of a 34-weeks pregnancy (26–27 weeks amenorrhoea). An X-ray was taken for evidence of foetal abnormality, as an excess of liquor amnii was suspected. No foetal deformity was detected, however. Another feature was the appearance of ecchymoses on the lower limbs. This was associated with a prothrombin activity of 42 per cent. It was thought that this might aggravate the bleeding from her haemorrhoids, which was still troublesome. Vitamin K_1 10 mg. was given by mouth; a week later the affected areas were less obvious. On 10th November there was an increase in β-globulin in the serum before albuminuria or other sign of pre-eclampsia appeared (Fig. 1). As such an increase is common in pre-eclampsia the possibility of this complication occurring was foreseen. When the proteinuria did develop, electrophoretic analysis showed the urinary protein to contain the β-globulin fraction (Fig. 2). Kelsey *et al.* (1955) mention a reversal of the albumin-globulin ratio in two of their non-pregnant cases and attribute it to the chlorpromazine. On 23rd November a slight rise in blood pressure was noted (135/85 mm. Hg). There was no albuminuria and no oedema. The blood pressure on 4th December was normal and a week later 140/80 mm. Hg. In November and December the patient complained of intermittent attacks of diarrhoea. This was probably partly due to her illness and partly to deviations from her diet. Faeces examined showed urobilin to be present in reduced amount; no organisms of the typhoid-dysentery group were cultured. In the first fortnight of December she had 3 attacks of "flushes", with sweating and faintness; there was no pyrexia. A gradual reduction in the prednisone was begun on 7th December and it was stopped on 22nd December. Jaundice and nausea continued.

As the pregnancy advanced the discrepancy between uterine size and duration of amenorrhoea became less obvious. At the 32nd week further areas of ecchymosis appeared on the lower limbs and chest wall. Vitamin K_1 was given again and repeated at intervals of about a week. On 28th December (33–34 weeks) protein was found in the urine and was present daily in varying amounts until after delivery. The amount in a catheter specimen of urine on 28th December was 7 g. per litre. Slight oedema was detected on 1st January, 1960, and this and the blood pressure increased. The latter was 170/100 mm. on 2nd January and the patient then complained of headache. On 4th January (34th week) surgical induction of labour was carried out because of the pre-eclamptic toxaemia. About 6 fluid ounces of dark green liquor amnii was obtained by Drew-Smythe catheter. A Fouchet's test done on the liquor amnii was weakly positive for bilirubin. The prothrombin activity at this time was 50 per cent. Labour began 21 hours later. Intravenous glucose (1 litre of 5 per cent) was given during labour. The patient delivered herself spontaneously of a living female child weighing 3 pounds after a labour lasting 3 hours 5 minutes. The baby had a mongoloid appearance at birth and further observation has confirmed the diagnosis of mongolism. The child's haemoglobin was 15·8 g./100 ml. at birth. Her blood groups were "A", Rh positive, and the Coombs test was negative. The third stage of labour was complicated by a post-partum haemorrhage of 30 fluid ounces. In the first fortnight of the puerperium there was excessive bleeding *per vaginam* with consequent anaemia. Blood transfusion, ergometrine and vitamin K_1 were employed. A small piece of placental tissue was passed on 9th January. A further piece was

removed under pudendal block analgesia supplemented by nitrous oxide and oxygen inhalation on 19th January. The uterus was explored at this time because a blood loss of about 13 fluid ounces occurred accompanied by normal clotting (prothrombin 100 per cent) and a rise of temperature. The latter was controlled by "crystamycin". Normal lochia and involution followed. All ecchymoses had cleared by 20th January. A week later the patient's appetite had greatly improved. By 14th February her haemoglobin was 11·7 g./100 ml., her jaundice had cleared, she was taking normal diet and gaining in weight. She was discharged from hospital.

When seen at the postnatal clinic on 9th March the patient felt and looked well. Her blood pressure was 140/100 mm. Hg. There was no proteinuria. Her stools and urine were of normal appearance. The results of liver function tests are shown in the table. Cholecystography was done on 17th and 18th March. The gallbladder was outlined and functioned satisfactorily. There was no stone. Further liver function tests done on 4th May are also recorded. Her blood pressure was 150/90 and her weight 125 pounds. The baby remains in hospital: her feeding is mainly by tube and weight gain is slow.

Discussion

The clinical features in this case are similar to those already described, namely: jaundice, pruritus, clay-coloured stools, nausea, vomiting, lethargy, anaemia and diarrhoea. An unusual feature was the fluctuation in the severity of the symptoms. Petechiae and ecchymoses accompanied the lowered prothrombin activity and may have been an aggravating factor in the bleeding from the haemorrhoids and the initial postpartum haemorrhage. The jaundice lasted for more than 6 months, clearing about 5 weeks after delivery. The duration of the jaundice in pregnant cases, as in other recorded cases, varies from several weeks to several months. It is interesting that in the case reported by Kinross-Wright and Moyer (1956) the jaundice developed about the third month and suddenly cleared two weeks before delivery. In most of the pregnant cases the patients have been free from symptoms before their confinements. No adverse effect on the child has been reported. A common finding is that clinical improvement precedes laboratory evidence of recovery. In the case of Elliott *et al.* (1955) cortisone was employed with benefit, but no significant clinical improvement followed its use in our case. Gebhart *et al.* (1958) did not consider steroid therapy to be of value. Several writers report the occurrence of rigors and pyrexia before the appearance of the jaundice. We did not obtain a history of these. There was only vague discomfort in the hepatic region in our case, and no enlargement of the liver.

The laboratory findings are in keeping with those found in this type of obstructive jaundice, viz., raised alkaline phosphatase, normal flocculation tests, normal serum protein and moderate increase in transaminases. There was an initial increase of the latter, followed by a fall. The behaviour of the transaminases suggests initial hepatocellular damage. The increase in alkaline phosphatase and cholesterol after delivery are difficult to interpret. There was no eosinophilia. Our case bears out Graham's (1959) statement that obstructive jaundice in a patient who has received chlorpromazine is more likely to be due to the drug than to a neoplasm or calculus. We did not employ liver biopsy, nor resort to laparotomy.

Most of the writers quoted advise caution in the use of chlorpromazine. The prognosis where jaundice occurs is good except where there is pre-existing liver or kidney disease. Nevertheless, several months of incapacity may follow the use of the drug and unnecessary abdominal operations be performed. It is possible that the complication is more common in pregnancy than the literature on the subject suggests. There is also reason to believe that chlorpromazine is being more widely used than formerly in obstetrics. If this is so, an increased incidence of jaundice is bound to follow. In our opinion there is seldom, if ever, justification for the use of chlorpromazine in obstetrics. This is in accord with the view expressed by Hodges and Bennett (1959) who are concerned particularly with the use of the drug in obstetric analgesia and anaesthesia.

Summary

A case of chlorpromazine jaundice occurring at the third month of pregnancy is described. The pregnancy was complicated by pre-eclamptic toxaemia and labour was induced for this reason at the 34th week. The jaundice lasted for more than 6 months, and 3 months after delivery the liver function tests were still abnormal. There was no adverse effect on the child. It is recommended that chlorpromazine administration be avoided in obstetrics.

Acknowledgments

We are grateful to Dr. B. B. MacGillivray, late Medical Registrar, Stepping Hill Hospital, for his assistance in the care of this patient, and to the Librarian of the British Medical Association for his help in the search for references.

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PRIMARY ABDOMINAL PREGNANCY

BY

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ALTHOUGH there have been a few authentic cases of primary abdominal pregnancy reported in the literature, the possibility of primary peritoneal implantation of the ovum is still doubted by some authors. Jeffcoate (1957) states that it is extremely doubtful if primary abdominal pregnancy ever occurs. Prior to the case reported by Studdiford (1942), which was accepted by the Society of Gynecological Pathologists of New York as representing a primary peritoneal pregnancy, Novak (1940) had denied the possibility of this type of extra-uterine gestation. In Studdiford's case the nidation site of a 28-day ovum was on the peritoneal surface of the posterior wall of the uterus, 1½ cm. medial to the insertion of the left tube. It was unfortunately closely adjacent to the interstitial portion of the tube and, although there was no demonstrable communication, it is understandable that this case might not be convincing to all gynaecologists.

Much more convincing are the cases reported by Steptoe (1950) and Myles (1954). In both, the patients had had 5½-weeks amenorrhoea and the site of implantation in Steptoe's case was the base of the left broad ligament close to the uterus. In Myles' case the ovum had implanted on the posterior surface of the uterus just medial to the left utero-sacral ligament. The uterine tubes were quite normal in both cases.

More recently, Ahnquist and Lund (1955) have described a 25–27-day ovum which was found on the peritoneal surface of an occluded Fallopian tube.

Undoubtedly these are authentic cases and satisfy the criteria for primary abdominal pregnancy proposed by Studdiford (1942) which are as follows:

(1) That both tubes and ovaries are normal with no evidence of recent or remote injury.

(2) Absence of any utero-peritoneal fistula.

(3) The presence of a pregnancy related exclusively to the peritoneal surface and young enough to eliminate the possibility of secondary implantation following a primary nidation in the tube.

The earlier an abdominal pregnancy can be detected, the more convincing will be the evidence in favour of primary peritoneal implantation and the possibility of early secondary implantation will be ruled out.

The following report of a 23-day pregnancy is presented as positive proof for the occurrence of primary peritoneal implantation.

CASE REPORT

Mrs. M.M., a primigravida, aged 25 years, was admitted to the Royal Victoria Hospital, Belfast, as an emergency on 24th April, 1959. Her menstrual periods were irregular but some bleeding, thought to be a normal period, had occurred on 31st March, 24 days before her admission to hospital. She had had no previous illnesses or operations.

One week before admission she had noticed deep pelvic pain on intercourse. Two days before admission she experienced a short bout of crampy lower abdominal pain which quickly settled. On the day before admission she had slight diarrhoea and again experienced acute

FIG. 1

Primary abdominal pregnancy. Photograph of intact chorionic vesicle after clearing it of blood clot. ×5·1.

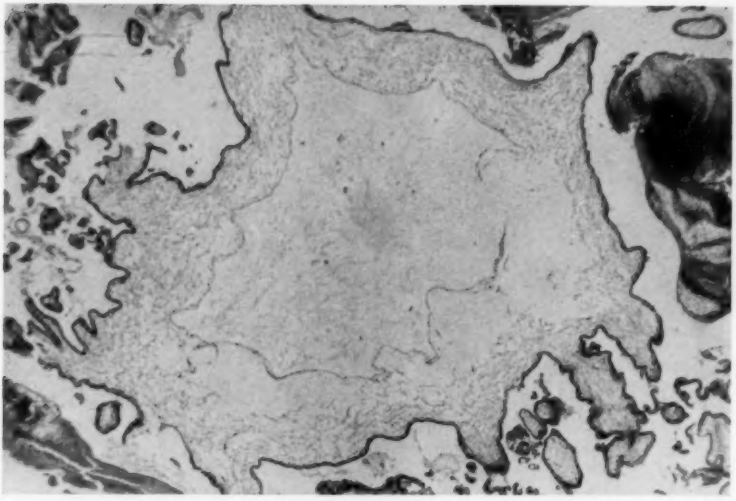

FIG. 2

Photomicrograph of entire chorionic vesicle. Heuser's membrane in the blastocyst cavity is clearly seen. ×25·8.

FIG. 3

Higher power photomicrograph showing details of the villous sprouts. ×152.

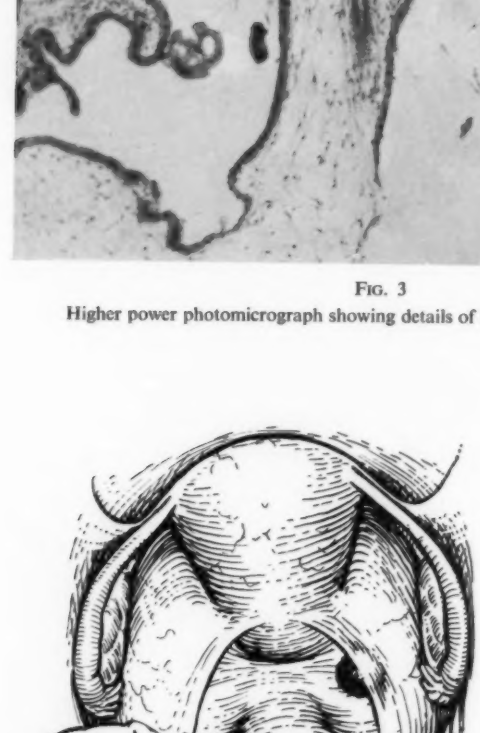

FIG. 4

Diagrammatic representation of the 23-day pregnancy as seen at laparotomy situated below the right utero-sacral ligament.

W.G.M.

dyspareunia. At midnight she developed acute lower abdominal pain and vomited several times. She was seen by her family doctor in the morning and the pain was now generalized all over the abdomen. He elicited acute abdominal tenderness and noted some distension.

On arrival at the hospital, the patient was admitted to the surgical wards for observation. At that time her pulse rate was 92/minute, temperature 98° F. and blood pressure 105/70. She was pale and anxious, general abdominal tenderness was elicited and there was acute tenderness on vaginal examination. Shortly after admission, her condition became much worse and she complained bitterly of acute pain in both shoulders. She was immediately transferred to the gynaecological wards.

On examination, the patient looked desperately ill with extreme pallor and an expression of terror. Her pulse rate was 120/minute and blood pressure 90/50 mm. Hg. The abdomen was acutely tender with board-like rigidity and her knees were drawn up. Acute pain in both shoulders was still present.

A diagnosis of ruptured ectopic pregnancy was made, blood transfusion was immediately commenced and the patient was quickly transferred to the operating theatre.

Under general anaesthesia, a vaginal examination disclosed a small nodule in the right fornix and a cystic left adnexal swelling. The uterus was normal in size, anteverted and mobile.

At laparotomy the peritoneal cavity was found to be filled with bright red blood. Approximately 4 pints (2 litres) were removed by suction. Both Fallopian tubes were normal. The left ovary contained a thin-walled follicular cyst, about 2 inches in diameter, which was easily ruptured. A smaller cyst was present in the right ovary. The cause of the intra-peritoneal bleeding remained obscure for some time until, after a careful search throughout the entire abdomen, a small reddish-purple nodule little larger than a pea was found on the right side of the pouch of Douglas below the utero-sacral ligament (Fig. 1). There was continuous bleeding from this nodule and further inspection revealed that it was a tiny villous sac surrounded by blood clot. It was easily shelled out with a finger, and the bleeding site of implantation was closed with a continuous catgut suture. This satisfactorily arrested the bleeding, the abdomen was cleared of all remaining blood and blood clot and closed in layers. Six pints of blood were transfused during and after the operation.

The patient made an uneventful recovery and was allowed home on the 9th post-operative day.

Description of the Specimen

The specimen was immediately sent to Dr. Morton, embryologist, Queen's University, for detailed study. Photographs were taken of the intact blastocyst after clearing the blood clot away from it (Fig. 1). Serial sections of the blastocyst were made and studied histologically (Figs. 2 and 3). The measurements of the specimen were as follows:

External diameters of the chorionic vesicle floating in fluid: 15×12 millimetres.

Measurements from the microscopic preparation:

External: $7 \cdot 4 \times 4 \cdot 73 \times 8 \cdot 16$ (thick) millimetres.

Internal: $3 \cdot 0 \times 2 \cdot 0 \times 4 \cdot 3$ (thick) millimetres.

The estimated age of the blastocyst is 23 to 24 days.

Comment

The irregular menstrual history of this patient did not help in assessing the gestation period but the embryological age was 23-24 days. If the slight bleeding noted 24 days before the patient's admission to hospital had been associated with ovulation then the calculated duration of the pregnancy would agree with the embryological age.

An additional feature supporting the primary implantation below the right utero-sacral ligament was the dyspareunia that had occurred one week before admission. This must have been due to the misplaced pregnancy, then just over two weeks old. The patient had never previously experienced dyspareunia.

Careful examination of the pelvic peritoneum did not disclose any areas of endometriosis, the presence of which is reputed to favour primary peritoneal implantation of the ovum.

Summary

(1) A 23- to 24-day pregnancy implanted on the peritoneum below the right utero-sacral ligament is described and it is considered to be positive proof for the occurrence of primary peritoneal implantation.

(2) It is believed that this is the youngest primary peritoneal pregnancy to be recorded.

ACKNOWLEDGMENTS

I am indebted to Dr. W. R. M. Morton of the Embryology Department, Queen's University, for his studies, photographs and comments on the specimen, and to Mr. George Ae. Smith, Medical Artist, Royal Victoria Hospital, for his drawing representing the pregnancy as seen at laparotomy.

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BLOOD GROUP INCOMPATIBILITY AS A CAUSE OF SPONTANEOUS ABORTION

BY

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THE following work was carried out in the Gynaecology Department of Royal Perth Hospital and the Obstetrics Department of King Edward Memorial Hospital for Women, Perth, Western Australia.

Spontaneous abortions may result from random or fortuitous factors, which may not repeat themselves in a succeeding pregnancy; or it may result from a recurring factor, inimical to the growth of the foetus. It is thought that at least half of all spontaneous abortions occur due to some defect of the embryo, but it is important to realize that not all these defects are due to a genetic influence. Some abnormality of maternal environment may play a large part in the defective growth and development of a foetus and thus initiate an abortion.

It is this abnormality of maternal environment that we are at present interested in and in this paper we are drawing particular attention to certain blood group factors and their relationship to abortions.

REVIEW OF PREVIOUS INVESTIGATIONS

As long ago as 1925 Hirzfeld and Zborowski investigated groups of married people, and their children. They found that there was a relative deficiency of blood group A children in families where the mother is blood group O and the father is blood group A.

Then Levine (1943), Sjöstedt, Grubb and Linell (1951), Grubb and Sjöstedt (1955), and Matsunaga and Itoh (1958) carried out studies on groups of families in respect to spontaneous abortions. Their collective evidence showed that there was a slight increase in the number of spontaneous abortions in those marriages where incompatibility existed between the ABO blood groups of the partners. They also suggested that sterility may be due in some part to the incompatible blood group matings of the partners.

In 1936 Jonsson investigated mothers who had recently had infants. Mollison quotes Jonsson's findings as follows: In 594 mothers with blood group O, there were anti-A or anti-B haemolysins present in 14·5 per cent of the sera. By contrast in 636 group O men he found iso-haemolysins present in only 3·5 per cent of the sera.

The relationship of the iso-haemolysins to a previous heterospecific pregnancy was strikingly shown when the infant's blood group was also taken into account. Thus, in mothers with O children the incidence of haemolysins was 7·1 per cent; in those with B children it was 20·8 per cent, and in those with A children, 28·1 per cent. From Jonsson's findings it becomes

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apparent that marriages between parents where there is blood group incompatibility lead to a higher frequency of haemolysins after a pregnancy.

Rachel Jacobowicz (1956) carried out further confirmatory work along these lines, and taking unselected females she found that only 5·3 per cent had haemolysins present in their sera. These results are comparable to the 3·5 per cent haemolysins in males, in Jonsson's series.

Of considerable importance is also the occurrence of successive miscarriages in cases where anti-Tj^a antibodies were detected in the maternal serum. This antibody is now recognized to be part of the P blood group system (Sanger, 1955) and Race and Sanger (1958) consider the haemolytic potentiality of this antibody to be more violent than anti-A or anti-B .

Studies by Levine and Koch (1954) and Iseki, Masaki and Levine (1954) have shown an interesting relationship between the presence of anti-$P+P_1$ and habitual abortions. Eighteen miscarriages were reported in five individuals with this antibody present in their sera. Other examples which relate the presence of anti-$P+P_1$ to spontaneous abortions have been reported by Zoutendyk and Levine (1952), Hirzfeld and Grabowska (1952) and Walsh and Kooptzoff (1954).

Our observations suggest that blood group factors other than anti-A or anti-B may be concerned in the aetiology of spontaneous abortions and it is our intention here to examine some of the factors that might be responsible.

If in fact there is some blood group incompatibility present in the maternal serum to explain a miscarriage it might act at the placental barrier in one of two ways.

(*a*) There could be tissue cell destruction by a maternal haemolysin, the maternal haemolysin being produced as a response to foetal substance passing across the placenta. If sufficient tissue cell destruction takes place then an abortion might result.

(*b*) The haemolytic factor produced by the mother might act directly on foetal red cells causing death of cells. This cellular destruction might be in the foetus or could be in the placenta itself.

To substantiate these two views, a recent paper by Freda (1958) in New York has shown that foetal substance does pass across the placental barrier and that maternal blood group substances can be found on the foetal side of the placenta. Freda has postulated that this might be the mechanism responsible for haemolytic disease of the newborn. It appears likely, that if this is the mechanism for haemolytic disease of the newborn then it could also be the mechanism whereby spontaneous abortions occur. As blood group substance only is involved and not red cells then this type of reaction could occur during a first pregnancy, and would explain habitual abortions and abortions occurring at first conception.

Mollison and Thomas (1959) in a recent paper have shown that many blood group antibodies, which do not haemolyze red cells *in vitro* under normal conditions, do have haemolytic potentiality when examined by special methods using animal complement. In other words there are many haemolysins present not related to the A or B blood group systems which are not easily detected. These haemolysins might be present in easily detectable amounts immediately after an episode of immunization but quickly revert to their normal state. This would explain the transient nature of some potent haemolysins which are often found soon after an episode of immunization but which completely disappear several days later.

Plan of Investigation

In this series, we have investigated the relationship of abortions to the incompatible blood group matings ABO and have made a special investigation of haemolysins related to this and other blood group systems.

Primarily, the haemolysins we paid particular attention to were those related to the group A and B system but towards the latter part of our work, we looked for haemolysins in connexion with abortion not related to blood groups A and B.

Other evidence that could be related to the aetiology of spontaneous abortion has been noted, and, where relevant, we have included the information in this report.

Material and Methods for Investigation

Abortion Series

The cases for investigation were carefully selected by one of the authors (B.G.W.) working in the Gynaecology Department of Royal Perth Hospital. The cases were women who had had spontaneous abortions, of unknown origin, where no more than three live births had occurred before the first miscarriage. These selected cases came from three groups.

(1) Routine abortions admitted to the hospital between 1st July, 1959 and 30th June, 1960. There were 268 cases of abortions admitted to the hospital during that time, and of these, only 60 were suitable for investigation.

(2) Over 250 letters were sent to women who had abortions in the hospital before July, 1959 and who were thought to be suitable for our series. Forty-eight of these women who attended with their husbands were subsequently examined and investigated. Only those cases who were genuinely interested in determining the cause of their abortion, attended after receiving our letter.

(3) We were fortunate to be able to collect 14 cases suitable for investigation from couples sent in by private practitioners. Altogether then our series consisted of 122 cases of spontaneous abortion. The criterion of selection was particularly severe, and many were excluded on a minor point.

If any local cause such as fibroid or retroverted uterus was found, the case was excluded even though these are not generally accepted as causes of abortion. A history suggestive of cervical incompetence was also grounds for exclusion.

In taking histories from our patients, the relevant facts obtained include the age of both couples, the length of marriage, number of children and their ages, number of abortions and the length of each pregnancy terminating in an abortion.

Control Group

As a control group we took 100 people who had never had an abortion and had at least 2 or more children.

These cases were taken from normal deliveries at King Edward Memorial Hospital or from among friends of the authors. No other selection was used for inclusion in this group.

Blood and saliva was taken from both husband and wife and subjected to the same series of investigation as for the abortion series.

Serological Procedure

Blood was collected from both partners in the marriage in 10 c.cm. amounts as whole blood and saliva in 5 c.cm. amounts. Saliva samples were immediately placed in a boiling water-bath for 20 minutes. Serum was separated from the blood clot within two hours after collection and stored at $-20°$ C. when not used for immediate testing.

Determination of A_1, A_2, B and O Blood Groups

A saline suspension of red cells was used to determine the ABO blood groups using standardized anti-A, anti-B and anti-A+B testing serum from the Commonwealth Serum Laboratories. The evaluation of subgroups A_1 and A_2 was determined using a standardized preparation of Lima Bean extract kindly donated by Dr. P. Brain, Director of the Red Cross Blood Transfusion Service, W.A. Division. All agglutination tests were carried out using the moist-chamber and flat glass-plate technique.

Determination of Saliva Secretor Status

To one drop of saliva was added one drop of saline agglutinating anti-A and another drop to anti-B and another drop to standardized anti-H (Ulex Europaeus extract). As a control, one drop of saline is added to one drop of anti-A, anti-B and anti-H serum. The drops are mixed with a clean glass rod and the plates placed in a moist chamber at room temperature for 15 minutes. At the end of this period one drop of a 5 per cent saline suspension of thrice-washed A_1, B and O cells is added to each of the saliva-serum mixtures and to the control. The plate is replaced in the moist chamber and left undisturbed for a further 30 minutes at room temperature. If the saliva inhibits the reactions of the anti-serum and the control does not, the saliva is said to be from a secretor.

The Evaluation of Haemolysins

(a) *Iso-haemolysin procedure for the A_1 and B blood group factors.*

All samples of serum independent of their blood group status were examined by the following procedure for the presence of A_1 and B haemolysins. As every sample of serum tested was less than 24 hours old their own complement activity was utilized to initiate red cell haemolysis. Each sample of serum was diluted by an equal volume of saline and three test tubes of diluted serum were prepared.

A 1 per cent suspension of thrice-washed group A_1, B and O cells was prepared and one volume of group A_1 cells was then added to the first tube, one volume of B cells to the second tube and one volume of O cells as control to the third tube. The test tubes are then incubated at 37° C. for 2 hours. At the completion of the incubation period the test tubes were centrifuged and the degree of haemolysis is read by holding the test tube in a good light.

(b) *Iso-haemolysin procedure for factors not related to the A and B blood group system.*

In this study it was of primary importance to isolate haemolysins not related to the blood group factor A and B. For this purpose we selected group O cells with the following blood group systems present: MNSs, P, Lutheran, Kell, Lewis, Duffy and Kidd. The same blood group donors were used throughout the procedure to eliminate possible variations.

The technique for this haemolysin test differs from the method used for the blood group A and B systems. The thrice-washed cells in saline were first sensitized with the serum (undiluted) at 5° C. (ice water-bath) for 1 hour, followed by a 1-hour incubation period at 37° C. (water-bath). At the completion of this final incubation period the test tubes were centrifuged and the degree of haemolysis examined in the usual manner.

Positive results obtained by this procedure have so far not been re-tested to determine the specificity of the haemolysin, but further studies will be carried out in the future to complete this aspect of the investigation. For the present a positive haemolytic reaction will simply be referred to as haemolysins not related to blood group A or B.

Results

(1) *The Distribution of ABO Blood Groups and Saliva Secretions Status*

Table I tabulates the distribution of the ABO blood groups and saliva secretion status of the abortion and control series investigated. For comparative purposes we have also included the blood group frequencies of 6,121 maternal bloods tested in this laboratory and reported

TABLE I

A_1, A_2, and O Blood Group Distribution and Saliva Secretor Status of Abort and Control Series

		Blood Groups						Saliva Secretor Status				Total Numbers Tested
		A_1 and A_2	A_2	B	O	A_1B and A_2B	A_2B	Secretor of ABH Sub-stances		Non-secretor of ABH Sub-stances		
		Number and %	Number and %	Number and %	Number and %	Number and %	Number and %	No.	%	No.	%	
Abort Series	Mother ..	47=38%	5=10%	10= 8%	61=50%	4=3%	2=50%	88	73	34	27	122
	Father ..	56=45%	5= 9%	12= 9%	51=41%	3=2%	1=33%	90	76	32	24	122
Control Series	Mother ..	47=47%	13=27%	10=10%	40=40%	3=3%	— —	77	77	23	23	100
	Father ..	35=35%	8=17%	11=11%	51=51%	3=3%	2=66%	75	75	25	25	100
Abort and Control Series combined		185=41%	31=17%	43= 9·7%	203=45%	13=2·9%	5=38%	330	75	114	25	444
Maternal blood groups from K.E.M. Hospital Series as quoted by Kirk *et al.* (1953)			41·8%		10·3%	44·8%	3·1%					6,121

by Kirk, Kirk and Stenhouse (1953) in a previous communication. When the blood group frequencies of 6,121 hospital cases are directly compared with the combined distribution of the ABO blood groups recorded on the abortion and control series no significant variation can be noted. This comparison shows the uniform distribution of our abortion and control series when compared with a larger group of cases from the same population.

Comparing the blood group distribution of the abortion series with the recorded findings of our Control group, some variation particularly in the distribution of blood groups A and O can be noted. In the abortion series a greater percentage of mothers are group O than in the Control group. On the other hand a greater proportion of fathers in the abortion series are group A than in the control series. The number of cases investigated is however too small to warrant any further discussion for this type of comparison.

The combined distribution of the A_1 and A_2 blood groups of mothers and fathers within the abortion and control series is however of particular interest. Table I shows that the A_2 blood group distribution is considerably less in the abortion series than the observed frequency in the control group (9·5 per cent as opposed to 24·5 per cent). The significance of this marked variation is at the present not very clear but the findings would suggest that the A_2 gene is of no consequence within the abortion series.

Also, from Table I it can be seen that the distribution of the saliva ABH secretor status in the two categories does not show a great deal of variation and would indicate that the presence or otherwise of blood group substances in the saliva is of no importance. It is possible however that quantitative differences exist within these two series as suggested by McNeil *et al.* (1960) but further studies will be necessary to confirm this view.

(2) *ABO Incompatibility and Abortion Rate*

In common with general usage we have considered a marriage to be incompatible, with regard to its blood groups, when the husband's red cells contain some blood group factor not demonstrable in his wife.

In the English and Australian populations the rate of incompatible marriages has been estimated to be 35 per cent. From Table III we see in our own control group that incompatible marriages occurred in 30 per cent of families. This figure is closely allied to the expected rate. However, on looking at our abortion group (Table II) we see that 45 per cent of the marriages were incompatible. This higher rate of incompatible marriages in the abortion group is to be expected and has been confirmed by previous investigations (Sjöstedt, Grubb and Linell, 1951; Matsunaga and Itoh, 1958).

When comparing the incompatible matings with the compatible matings in our abortion group (Table II) we see that the mean rate of abortions per family in the incompatible group is also higher than the mean values recorded for the compatible series (see Table II). Our observations show that the mean number of abortions experienced in the incompatible group is 2·3 per family as opposed to 1·9 abortions per family in the compatible group. These figures substantiate quite closely the work done by Sjöstedt *et al.*, and also by Matsunaga and Itoh. The cause of this increased abortion rate is evident when we examine the frequency of haemolysins present in each group.

(3) *Significance of Haemolysins*

The present study has recognized two varieties of haemolysins, the more common type associated with the blood group antigens A and B and those not related to these factors. The latter varieties were observed by using selected group O cells.

For comparative purpose we therefore discuss the more common variety first. From Table II we can see that the overall frequency of anti-A and anti-B haemolysins present in 122 cases of abortions is 45 per cent. This figure is in marked contrast to our control series of mothers in which the overall recorded percentage of anti-A and anti-B haemolysins is only 6 per cent.

If we differentiate the abort series into two categories, (*a*) those compatible and (*b*) incompatible for blood groups A and B, an even greater difference can be noted (see Table II). In the incompatible group we now recognize 76 per cent of mothers to possess anti-A or B

TABLE II

Abortion Series

ABO Blood Group Combinations Mother—Father	Number of Families	Number of Liveborn Infants	Number of Abortions	Haemolysins in Maternal Serum		Number of Families in Which No Haemolysins were Detected
				Specific for A_1 and B Cells Not O	Possessing Haemolytic Potential for Selected Group O Cells	
Incompatible:						
O × A_1	33	61	72	27	3	5
O × A_2	1	4	3	–	–	–
O × B	4	2	9	4	1	–
O × A_1B ..	1	1	8	1	–	–
A_1 × B	7	8	15	4	3	2
A_2 × B	1	2	5	–	–	1
B × A_1	6	12	9	4	1	2
A_1 × A_2B	1	2	3	1	–	–
A_2 × A_1B	1	1	4	1	–	–
Total	55 (45%)	93 1·6 per family	128 2·3 per family	42 (76%)	8 (14%)	10
		221—4·0 per family		45 (82%)		
Compatible:						
O × O	22	37	41	13	4	6
A_1 × O	23	39	50	–	5	18
A_2 × O	1	1	1	–	–	1
B × O	4	5	9	1	1	3
A_1B × O	1	–	3	–	–	1
A_1 × A_1 ..	7	12	9	–	2	5
A_2 × A_1 ..	2	3	3	–	–	2
A_1 × A_2 ..	4	8	7	–	1	3
A_1B × A_1 ..	1	–	3	–	1	–
A_2B × A_1 ..	2	1	4	–	1	1
Total	67	106 1·5 per family	130 1·9 per family	14 (21%)	15 (22%)	40
		236—3·5 per family		27 (40%)		
Grand Total ..	122	199 1·6 per family	258 2·1 per family	56 (45%)	23 (18%)	50
		457—3·7 per family		72 (59%)		

TABLE III

Control Series

ABO Blood Group Combinations Mother—Father	Number of Families	Number of Liveborn Infants	Haemolysins in Maternal Serum		Number of Families in Which No Haemolysins were Detected
			Specific for A_1 and B Cells Not O	Possessing Haemolytic Potential for Selected Group O Cells	
Incompatible:					
O × A_1	13	40	2	1	11
O × A_2	2	5	–	–	2
O × B	5	18	2	–	3
O × A_2B	1	3	–	–	1
A_1 × B	2	5	–	–	2
A_2 × B	2	4	–	–	2
B × A_1	3	9	–	–	3
B × A_2	2	4	–	–	2
Total	30 (30%)	88 2·9 per family	4 (13·3%)	1 (3·3%)	26
			4 (13·3%)		
Compatible:					
O × O	20	61	2	1	18
A_1 × O	21	70	–	1	20
A_2 × O	6	17	–	–	6
B × O	3	8	–	–	3
A_1B × O	1	4	–	–	1
A_1 × A_1	8	26	–	–	8
A_2 × A_2	3	6	–	–	3
A_1 × A_2	4	14	–	–	4
A_2 × A_2	1	4	–	–	1
A_1B × A_1B	1	3	–	–	1
A_1B × B	1	2	–	–	1
B × B	1	2	–	–	1
Total	70 (70%)	217 3·1 per family	2 (2·8%)	2 (2·8%)	67
			3 (4·3%)		
Grand Total	100	305 3·0 per family	6 (6%)	3 (3%)	93
			7 (7%)		

haemolysins as opposed to 21 per cent in the compatible group of the abort series. This significant increase in haemolysins, present in the incompatible matings having abortions, would tend to incriminate the presence of haemolysins as a factor in spontaneous abortions.

Compared with the control series of ABO incompatible mothers (see Table III) who have not experienced any abortions the above difference is even more marked. In the control incompatible matings we recorded only 13·3 per cent of anti-A and anti-B haemolysins, a percentage which is very similar to the observed frequency of 14 per cent reported by Jonsson (1936) in his survey. Similarly, the ABO compatible groups had only 2 mothers in 70 with A and B haemolysins present. This 2·8 per cent is also almost identical with the observation of Jonsson (1936) and Jacobowicz (1956).

The increased occurrence of anti-A or anti-B haemolysins in the incompatible abortion group does not explain the high abortion rate in the ABO compatible mating group (see Table II). Accordingly we looked for the presence of haemolysins not related to the ABO blood group system. If our reasoning was correct and we assumed that the presence of haemolysins could be the cause of many spontaneous abortions we should also find a significant increase in haemolysins not related to the ABO systems.

The reported association of anti-P+P_1 haemolysins in habitual aborters by Levine (1943), Levine and Koch (1954), Iseki, Masaki and Levine (1954), Zoutendyk and Levine (1952) and Walsh and Kooptzoff (1954) led us to believe that other incompatibility systems could influence the spontaneous abortion rate and our present study was therefore also directed to investigate the frequency of haemolysins other than anti-A or anti-B.

The exact nature or specificity of these haemolysins has so far not been determined. The fact that haemolysins could be recorded with a procedure which recognized blood group systems other than the commonly known factor A or B was thought to be sufficient for this investigation. In this communication we intend for the present to refer to these haemolysins as haemolysins not related to A and B blood group antigens. The recorded findings on Table II and Table III show that this type of haemolysin has been found in the abort as well as in the control series of maternal bloods. The presence of haemolysins which are not related to the A and B blood group system is however greater in the abort series than the controls. The abort series showed a frequency of 18 per cent as opposed to only 3 per cent in the control group.

Of particular interest with regard to haemolysins which were not related to the A or B blood group system was our observation that these haemolysins occurred more frequently in the ABO compatible mating group. This would indicate that they have their greatest influence only on those cases where the ABO haemolytic system has not already caused an abortion.

When we compare the combined frequency of haemolysins, including those active for A and B antigens (see Table IV), we can recognize 59 per cent of mothers in the abort series to possess a haemolysin which is in marked contrast with the observed findings of only 7 per cent in the control group. These results beyond any doubt associate the presence of haemolysins with spontaneous abortions.

(4) *Sterility and Infertility*

Previous authors have stated that the marriage of ABO incompatible partners leads to a higher incidence of sterility and infertility. In our own series of cases we found that a total of 231 pregnancies (abortions and live births) occurred in our incompatible abortion group, where 55 matings were concerned. This represents a total of 4·0 pregnancies per family (see Table II).

In our control group of incompatible matings we found that 88 infants were born to 30 matings, or 2·9 per family (see Table III). When these two groups of people are compared with compatible matings we see similar figures. There was a total of 226 pregnancies (abortions and live births) in our compatible abortion group where 67 matings occurred. This represents a rate of 3·3 pregnancies per marriage. In our control group of 70 compatible marriages there were 217 live births or 3 pregnancies per family.

From the above figures it becomes apparent

TABLE IV

Summary of Results on Abort and Control Series

	Abort Series Number of Families—122	Control Series Number of Families—100
Mean number of livebirths	1·6 per family	3·0 per family
Mean number of abortions	2·1 per family	Nil
Mean number of pregnancies	3·7 per family	3·0 per family
Overall percentage of haemolysins present in maternal serum	59%	7·0%

that the mating of incompatible parents does not lead to a higher incidence of infertility and probably not to sterility. The higher incidence of pregnancies per marriage in the abortion group can be accounted for by the increased desire for more children after repeated abortions, but at no time were we able to substantiate the theory of other writers that there may be an intrauterine selection prior to conception taking place.

(5) *Chorionic Gonadotrophins and Haemolysins*

In collaboration with our colleague Dr. L. H. Jorgenson, who is at the present engaged in the study of chorionic gonadotrophin levels in abortions we investigated the *in vivo* and the *in vitro* effect of chorionic gonadotrophins and maternal haemolysins. *In vitro* experiments showed that preparations of chorionic gonadotrophins are capable of inhibiting the haemolytic potentiality of haemolysins. This suggested to us a mechanism whereby the chorionic gonadotrophins neutralize the haemolysins and so prevent an abortion. If for some reason the maternal level of chorionic gonadotrophins falls the haemolysin level rises and an abortion can take place.

To investigate this theory we have so far examined 56 women who were known habitual aborters. When they became pregnant the level of chorionic gonadotrophins and the presence of haemolysins were tested weekly. In the majority of cases when the gonadotrophin level was high, no haemolysins were detected. In those cases where the chorionic gonadotrophins level fell, haemolysins became apparent and remained so till either an abortion occurred or the gonadotrophin levels rose once again.

This curious effect between chorionic gonadotrophins and haemolysins is under further investigation and we merely present it as being causally related to spontaneous abortion.

DISCUSSION

The presence of haemolytic factors is postulated as a cause of some spontaneous abortions. It is probable that substances related to blood group factors from the foetus pass across the placenta by the mechanism described by Freda (1958), and that these substances evoke an antibody response in the mother. This antibody may be a transient haemolysin or have haemolytic potential only demonstrated by special techniques.

The haemolysins are then passed back across the placental barrier to cause red cell haemolysis or tissue destruction. This action could occur at a very early time *in utero* and would account for those spontaneous abortions occurring in the first few weeks of pregnancy.

The reason that a large number of women with haemolysins present do not have abortions every time can be explained in one of three ways:

(*i*) The haemolysins may not be present in sufficiently high concentration to cause any great amount of tissue destruction.

(*ii*) The foetus may be a secretor of the specific substance. In this manner, neutralization of the haemolysins and protection of foetal

tissue takes place (Vos and Kirk, 1958) to prevent overt destruction.

(*iii*) The foetus might be compatible with the mother; the haemolysins being caused by a previous pregnancy.

A fourth mechanism which might have some bearing is the neutralization potentiality of chorionic gonadotrophins for haemolysins. If for some reason the haemolysin level is raised so that all the gonadotrophins are utilized then abortion could occur, either due to cellular destruction by haemolysins or by the withdrawal of support of the necessary hormones.

Conclusion

From the material we have examined we found that there is a definite, but slight, rise in the number of abortions occurring in those matings where ABO blood group incompatibility existed. This increase in abortion rate was found to be associated with the presence of haemolysins in those mothers where incompatibility existed. From our findings we postulated that the haemolysins formed by the mother pass across the placenta and cause red cell and tissue destruction in the foetus. This mechanism is similar to that described by Freda (1958) to account for red cell destruction in haemolytic disease of the newborn.

We were also able to implicate haemolysins not belonging to the A or B blood group system and suggest that they play just as significant a role in the production of a spontaneous abortion as do the A or B haemolysins.

A further field for future investigation would be to examine all foetal tissue from spontaneous abortions and look specifically for haemolytic activity or cellular destruction. If this could be correlated with the presence of haemolysins it would conclusively implicate the haemolysin as an aetiological factor in a large number of abortions.

Summary

(1) We have presented a series of 122 marriages in which spontaneous abortions had taken place. This study has shown that there is a definite increase in abortion amongst those couples where ABO blood group incompatibility exists. Forty-five per cent of our 122 cases of spontaneous abortions had incompatible blood group matings as compared to 30 per cent in our control series.

(2) We also found that 59 per cent of our 122 mothers possessed haemolysins in their sera as compared to only 9 per cent in our control group.

Although the majority of haemolysins were found in the incompatible mating group of aborters (82 per cent) there were sufficient numbers in the compatible abortion group (40 per cent) to make us suspect that haemolytic systems other than the ABO factor are responsible for spontaneous abortions.

(3) The possibility of infertility and sterility due to ABO incompatibility was discussed and our figures indicate that there is probably no selection taking place before pregnancy occurs.

(4) The secretor status of the parents has been found to have no bearing on the outcome of the pregnancy.

(5) It has been found that the A_2 subgroup is probably not related to spontaneous abortion in the ABO incompatible matings.

(6) The relationship between haemolysins and chorionic gonadotrophins is discussed, and it is suggested that interaction between these two substances may be a causative factor in abortions.

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HAEMANGIOPERICYTOMA UTERI

BY

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VASCULAR tumours of the uterus are rare, and until 1955 Pedowitz, Felmus and Grayzel could find only 128 cases in the literature. Haemangiopericytoma, first described by Stout and Murray in 1942, is one of the most uncommon of these tumours and since that time only 27 examples in the uterus have been reported. A report of three more cases is presented now. Interest was stimulated by the first case, which exhibited clinical features hitherto unknown to the author. The nature of the second case was unsuspected before pathological examination and the finding of an area of haemangiopericytoma in the uterus removed from the third patient was incidental.

Case 1

Mrs. F.A., an Iraqui, aged 40 years, was admitted to St. George's Hospital on 9th October, 1954, complaining of irregular vaginal bleeding, a sero-sanguineous discharge and malaise. She had had three children, all normal confinements, and two miscarriages.

There was nothing of note in her past medical or family history prior to 1952, when she was seen by a gynaecologist in Baghdad with a history of several months of "profuse vaginal haemorrhage". Uterine fibroids were diagnosed and on 19th October, 1952, a subtotal hysterectomy with conservation of the ovaries was performed. Fibromyomata were said to involve the whole body of the uterus, but pathological examination of the operation specimen was omitted.

Subsequently she was well for two years and then again sought advice after an episode of severe post-coital bleeding. Examination revealed a polypoidal growth filling the vagina and a biopsy of this was reported as "granulation tissue". As much as possible of the mass was removed and it was noted that little bleeding occurred. Post-operatively 10 per cent silver nitrate was applied to the area on several occasions.

Five months later the patient again reported; this time with difficulty of micturition and dysuria. On examination the vagina was once again seen to be filled with a polypoidal mass and it was now feared that this was sarcomatous. The patient was transferred to London.

Examination on admission confirmed the presence of the vaginal tumour, which looked like a large piece of placenta filling the vagina. No other abnormality was detected on physical examination and X-rays of the chest, pelvis and lumbar spine were normal.

On 13th October, 1954 an examination under anaesthetic was carried out and a friable necrotic polypoidal growth was found, attached to the anterior and right lateral walls of the vagina and to the cervix. It extended to the lateral pelvic wall on the right side.

A biopsy specimen was taken and two ovoids, each containing 35 mg. of radium, were inserted in close proximity to the tumour mass and left *in situ* for twenty-four hours.

Pathological examination of the specimen taken by biopsy from the vaginal tumour revealed a highly cellular structure in which proliferating capillaries were surrounded by concentric groups of neoplastic cells. Reticulin was abundant and formed a distinct vascular pattern (Fig. 1).

On 20th October the application of radium was repeated under general anaesthetic. The tumour had decreased in size and as much as

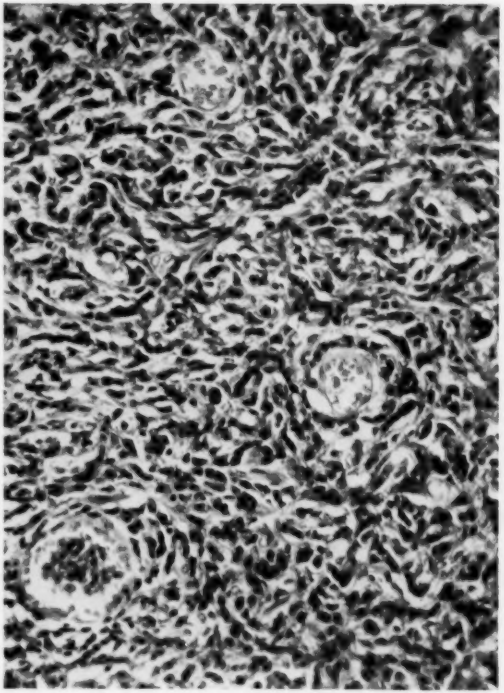

FIG. 1

Photomicrograph of a section from the biopsy taken from the tumour in the vagina under high power. This shows a highly cellular structure in which proliferating capillaries are surrounded by concentric groups of neoplastic cells.

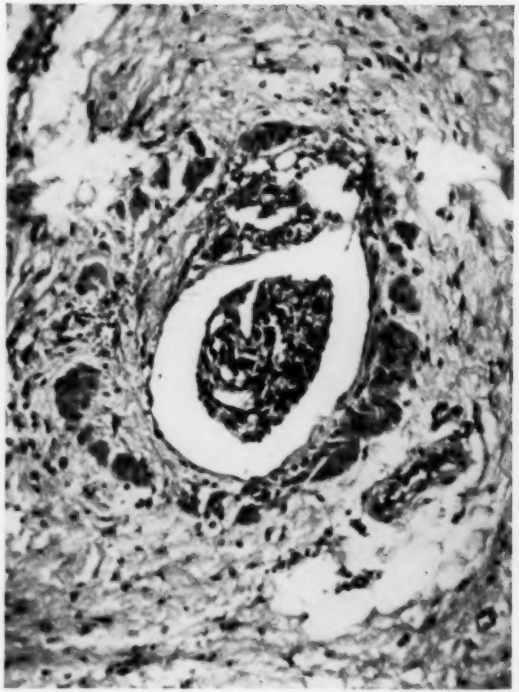

FIG. 2

Section under high power showing the lumen of a small vein filled with tumour tissue. H. & E. ×110.

FIG. 3

Photograph of the bi-sected uterus removed from Miss G.G. The tumour occupies the greater part of the myometrium and large areas of necrosis are present.

possible was removed with a diathermy loop. The cervical stump was included in one piece of removed tumour.

The haemoglobin had now fallen to 55 per cent and a blood transfusion was given.

A further examination under anaesthetic was carried out on 3rd November, 1954 and a mass was felt on the right side of the pelvis. This was thought to be an extension of the growth and laparotomy was decided upon. Proctoscopy was carried out and the rectum found to be free of growth.

An intravenous pyelogram on 9th November showed a non-functioning right kidney and a filling defect in the bladder, probably due to an extrinsic cause.

On 10th November laparotomy was performed, the abdomen being opened by a midline subumbilical incision. The main portion of the mass in the right side of the pelvis was found to be a right-sided ovarian cyst and this was removed, together with the other ovary. The tumour could be felt as a firm, rubbery mass occupying most of the vault of the vagina and very firmly fixed to the side wall of the pelvis on the right. The right ureter was very dilated, being constricted by tumour at its lower end. It was divided low down and re-implanted into the fundus of the bladder.

All tissue removed at operation was sent for pathological examination, including the terminal end of the right ureter. Histological examination showed invasion of the right ovary by growth. Much of the tissue was oedematous and areas of necrosis and haemorrhage were present. In several areas the tumour invaded the surrounding ovarian tissue. A moderate number of mitotic figures were present. The appearances were consistent with this being a metastasis but neither the gross appearance nor the histological appearances were such as to exclude the possibility that this tumour had arisen within the ovary. Haemangiopericytoma was present in the connective tissue around the right ureter and the lumen of a small vein in this area was completely filled by tumour tissue (Fig. 2).

The patient's progress was satisfactory and the treatment was completed by a course of deep X-ray therapy to the pelvis, a tumour dose of 3,000 r being given.

On 3rd January, 1955, cystoscopy was performed and this showed a normal bladder capacity. There was slight induration of the bladder on the right side, but no mucosal involvement. The transplanted ureter was patent and discharging urine.

The patient subsequently left England in good condition, with her vagina entirely free from growth. She has since remained well. The last report came from Iraq in the spring of 1960.

Case 2

Miss G.G., aged 51 years, a house parlourmaid. She was admitted to hospital on 6th September, 1960 with a lower abdominal mass which had been found on routine examination by a general surgeon, to whom she had been sent with a lump in the breast.

On direct questioning she stated that her periods had been heavier than normal during the previous twelve months. Her normal cycle was 5–6/28 and this had not changed, although her loss was heavier, with the passage of small clots. Intermenstrual bleeding had occurred on one occasion, two months prior to admission. The loss had been slight and lasted for one day.

For one year also she had complained of occasional griping pain in the lower abdomen. None of these symptoms had worried her and she had not mentioned them to her own doctor. Her bowels had remained regular and normal and she had had no urinary symptoms. Her appetite was good and she did not think she had lost weight.

In the past a simple cyst had been removed from her left breast in 1959 and in 1953 an appendicectomy had been performed.

On examination she was a fit-looking woman and the only abnormality found was a smooth swelling arising out of the pelvis in the midline to just above the level of the symphysis pubis. The patient was virgo intacta and bimanual rectal examination confirmed that the swelling was uterine in origin and a diagnosis of fibromyomata was made.

On 12th September, 1960 laparotomy was carried out through a right paramedian incision, the old scar of her previous appendicectomy being excised. The uterus was symmetrically enlarged to about the size of a twelve-weeks pregnancy, with a smooth surface, save for one small subserous fibroid. The ovaries and Fallopian tubes were normal. A few filmy adhesions were present in the pelvis. Total hysterectomy and bilateral salpingo-oöphorectomy were performed.

Post-operatively the patient's convalescence was quite uneventful and she was discharged from hospital on the 16th post-operative day.

On examination the uterus was found to measure 13×8×8 cm. and weighed 258 g. A round tumour occupied the major portion of the myometrium, which was soft, cream-coloured, with some central necrosis (Fig. 3). Microscopic examination showed that the tumour was a characteristic haemangiopericytoma, with some invasion of the myometrium but no subseral involvement. It was considered to be an actively growing tumour of a low-grade malignancy. The ovaries and Fallopian tubes were normal.

Case 3

Miss L.M., aged 53, a schoolteacher. She was admitted to hospital on 1st August, 1958, with a history of post-menopausal bleeding for six months. Her periods had ceased one year previously. There was no relevant past history and she was nulliparous.

A curettage was carried out and she was found to have a well-differentiated adenocarcinoma of the body of the uterus. After a preliminary insertion of radium, total abdominal hysterectomy and bilateral salpingo-oöphorectomy were performed. On routine histological examination of the operation specimen, a small, benign haemangiopericytoma was found embedded in the myometrium, in addition to the carcinoma of the body of the uterus. This tumour was obviously not producing symptoms and was occurring coincidentally with the carcinoma.

The patient remained well for two years, when she was re-admitted with severe upper abdominal pain and at laparotomy was found to have a large mass at the head of the pancreas with metastases in the liver. Biopsy showed this to be a mucus secreting adenocarcinoma of pancreatic origin.

Discussion

Stout and Murray (1942) first described a type of vascular tumour, composed of capillaries with one or more layers of round cells arranged about them. These perivascular cells distinguished such tumours, they believed, from capillary haemangiomata and were the pericytes of Zimmerman; contractile cells with long processes which are said to wrap themselves about capillaries and change the calibre of the lumen. They called this type of tumour haemangiopericytoma.

Since that time haemangiopericytoma has been reported in many organs—including the uterus, neck, tongue, popliteal space, triceps muscle, sigmoid colon and pericardium. De Sousa and Lash (1959) have recently published the first reported case of such a tumour of the vulva.

The uterus is one of the more common sites, but considerable confusion exists as to the relationship of these tumours to the neoplasms variously known as stromatous endometriosis, stromal myosis and endometrial sarcoma. This type of neoplasm was first reported by Doran and Lockyer (1909) who described "perithealiomatous" growths of the uterus, the cells of which resembled those of the stroma of the endometrium. Cases of stromatous or stromal endometriosis have since been reported by many writers, including in recent times Park and Tennent (1948) and Embrey (1952). Pedowitz, Felmus and Grayzel (1954, 1955) surveying reported cases of stromal endometriosis concluded that the majority of these cases were identical with, and should be re-classified as, haemangiopericytoma. Not all pathologists are in agreement with this view and Michaels and Langley (1957), reviewing 10 mesenchymal tumours of the uterus resembling haemangiopericytoma, stated that it was an over-simplification to consider stromatous endometriosis as a form of haemangiopericytoma, and they stressed the difficulty of exact diagnosis of undifferentiated mesenchymal uterine tumours. Some pathologists currently take the view that the two conditions are different and that both occur in the uterus. This view is supported by the description of haemangiopericytoma in many other organs in the body, whose histological appearance is identical to those found in the uterus.

Pedowitz *et al.* (1955), in their survey of vascular tumours of the uterus, concluded that haemangiopericytoma could be benign or malignant. Two of the 16 cases they reviewed died within 18 months of operation from metastases,

but another was living 11 years after the removal of the tumour by hysterectomy, although tumour cells were seen in the lymphatics on histological examination. In the first case reported above, the tumour was no doubt malignant, and it is interesting to note that the lumen of a small vein, removed with the lower end of the right ureter, was completely filled with tumour tissue. In both the first and second cases the patients complained in the first instance of abnormal uterine bleeding and fibroids were diagnosed. This is a fairly typical mode of presentation, and several of the reported cases were similarly mis-diagnosed prior to operation. According to Michaels and Langley (1957) these tumours often resemble, and may occur concurrently with, fibromyomata. Three of their cases presented with polypoid masses projecting through the cervix, as in the first case reported here.

Total hysterectomy and bilateral salpingo-oöphorectomy is the treatment of choice in early cases, and the excellent response to radiotherapy in the first case proves that the tumour may be radio-sensitive and that this form of treatment should be employed in cases where there has been extra-uterine extension of the growth. Pedowitz *et al.* (1955) stated that only 21 per cent of haemangiopericytomata occurring in all sites were malignant, and considered that in suitable cases local excision with conservation of the uterus might be justified in order to preserve fertility. However, this would seem to be rarely indicated as the malignant nature, or otherwise, of an individual tumour can only be established for certain by the subsequent course of the disease.

The histological diagnosis may be difficult, but it is aided by the use of special reticulum and connective tissue staining techniques. Silver staining will demonstrate uncanalized capillaries and the extra-luminal position of the pericytes.

Summary

Three cases of haemangiopericytoma are described, one of which recurred after subtotal hysterectomy and showed invasion of the cervical stump and one ovary and widespread infiltration of the vagina and parametrium, causing obstruction to the right ureter. Remission of the disease followed local removal, ureteric transplant and radiotherapy.

The difficulties of diagnosis and classification of these rare tumours are discussed, and it is suggested that they are not identical with stromatous endometriosis but are vascular neoplasms, occurring in the uterus as well as many other organs.

Acknowledgments

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HAEMANGIOPERICYTOMA OF THE UTERUS

A Case Report

BY

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HAEMANGIOPERICYTOMA is the name suggested by Stout and Murray (1942) for a vascular tumour characterized by numerous capillary blood vessels surrounded by one or more layers of rounded, oval or spindle-shaped cells. The tumours may vary in size from microscopic lesions to large masses, are slow growing and usually benign, though malignant cases occur. Fisher, Kaufman and Mason (1952) state that mitoses are present in malignant tumours. No true capsule is present, though compression of the adjacent tissue may give the appearance of a pseudo-capsule. The tumour may occur anywhere in the body. Histologically, many capillaries may be obvious on staining with haematoxylin and eosin, but numerous other collapsed vessels are shown up by using a reticulin stain which outlines the fibres outside the endothelial layer in the collapsed vessels. The endothelial cells are normal. Many of the capillaries contain red blood cells, but others appear empty. The tumour cells which surround and lie between the capillaries may have rounded to spindle-shaped nuclei. The amount of cytoplasm varies in the individual tumour cells. The reticulin stain also shows the individual tumour cells to be surrounded by a network of reticulin fibres (Green and Gerbie, 1954). The amount of collagen varies from tumour to tumour.

Occasional tumours of the uterus diagnosed primarily as cellular fibroid, stromatous endometriosis, haemangio-endothelioma and myosarcoma have on closer histological examination proved to be haemangiopericytomas.

Murray and Stout (1942) showed by tissue culture methods that the epithelial cell of the glomus tumour was the pericyte of Zimmermann, this cell being the contractile cell of the capillary. They suggested a relationship between the glomus pericytes and the tumour cells of the haemangiopericytoma. Further studies by Fisher, Kaufman and Mason (1952) by tissue culture methods on cells from haemangiopericytomas suggested that the epithelioid cells of the glomus tumour and the tumour cell of the haemangiopericytoma are probably identical and have a common origin, namely, the capillary pericyte. Also in 1942 Stout and Murray described tumours in several areas in which it was possible to trace a direct continuity between spindle cells without myofibrils and characteristic smooth muscle cells with definite myofibrils. They also state that transition forms containing immature fibrils can be identified. On the strength of these cases they suggest that the pericyte is a modified smooth muscle cell. In 1949 Stout published a study of 25 haemangiopericytomas from various parts of the body in order to establish the tumour as a definite entity.

Michaels and Langley (1957) state that Stout and Murray's hypothesis will be difficult to verify. They maintain that the similarity of the haemangiopericytoma to the epithelioid areas of the glomus tumour means no more than that both tumours are very vascular and composed of undifferentiated mesenchymal cells. On account of vascularity alone the isolation of pericytes by tissue culture methods is to be expected and is of doubtful significance as regards pathogenesis. They put forward as one of their hypotheses that the uterine haemangio-

pericytomatous pattern is merely a variant of a leiomyoma. They suggest as alternatives either that true haemangiopericytomas do occur in the uterus or that the pattern represents a reproduction of endometrial stroma. In one of the cases described by them an area typical of a haemangiopericytoma lies adjacent to an area typical of a fibroid. In 2 of the 5 cases described by Green and Gerbie (1954) the tumours were accompanied by histologically proven fibroids and other such tumours are described as being accompanied by fibroids though not proven histologically. Uterine fibroids are very common and subject to great histological variations. It is said that they may be vascular and on this account alone be mistaken for a haemangiopericytoma. Stout (1953) considers this source of confusion and suggests examination of the spindle cells for myofibrils in order to make the distinction. Difficulty arises here because in many fibroids, particularly in the presence of hyaline change, the muscle cells look atypical and lack myofibrils.

Park (1949) suggested that stromal endometriosis arises by a proliferation of precursor cells in the myometrium to form a tissue resembling endometrial stroma and Michaels and Langley (1957) have shown that this tumour has a haemangiopericytomatous appearance. Pedowitz, Felmus and Grayzel (1954) give their reasons for believing that the haemangiopericytoma of the uterus and those cases reported as stromal endometriosis are one and the same tumour, the latter having a vascular rather than a stromal origin.

Case Report

Mrs. S., aged 55 years, was first seen on the 28th October, 1959, complaining of postmenopausal bleeding. Her menopause had occurred in 1957. Examination revealed a bulky, anteverted uterus.

Investigations and Treatment

29th October, 1959. Ayre smear. No malignant cells seen.

12th November, 1959. Curettage performed. In the sections a few glands were present some showing mucinous degeneration. A small number of the glandular cells showed mitoses. The stroma was dense and very cellular. Much inflammatory exudate was present.

16th November, 1959. Total hysterectomy and bilateral salpingo-oöphorectomy was performed.

Gross Appearance of Specimen

The ovaries and Fallopian tubes were normal. The length of the uterus was 12 cm. The endometrium showed two areas of sessile hyperplasia, one near the internal os posteriorly, the other in the right lateral wall of the uterus near the fundus. At the fundus was an intramural fibroid 3 cm. in diameter. To the right of this was a large, intramural dumbbell-shaped tumour the cut surface of which was greyish-white and showed the presence of many blood vessels in certain areas. Arising from one half of this tumour was a small oval-shaped mass with an extremely vascular cut surface.

In the right paracervical region were two enlarged lymph nodes, the larger measuring 2 cm. in diameter and having a cut surface which was uniformly yellowish in colour, the other 1 cm. in diameter, its cut surface appearing extremely vascular.

Histological Features

The specimen was fixed in formol saline and sections of blocks from the uterine tumour, endometrial polyps, fibroid and paracervical nodules were stained with haematoxylin and eosin, van Gieson, Masson's trichrome and reticulin stains.

Sections of the polypoid areas of the endometrium showed numerous endometrial glands surrounded by a cellular stroma. The glands showed epithelial hyperplasia and some were dilated.

The fibroid showed the typical structure of smooth muscle fibres and large areas of hyaline connective tissue.

Several blocks were taken from the dumbbell-shaped tumour of the uterus. Routine haematoxylin and eosin stains showed the following main appearances:

(*a*) Cellular areas with but a few obvious capillary blood vessels (Fig. 1). The tumour cells were closely packed with little intercellular

matrix. The nuclei of these cells were round, oval or spindle-shaped, were of uniform pattern, had a fine chromatin network and a distinct nuclear membrane. Cytoplasm was absent or scanty in those cells with round or oval nuclei, but there appeared to be rather more in those with spindle-shaped nuclei. A few capillary blood vessels were obvious, some of these being surrounded by several layers of tumour cells (Fig. 2). The staining of corresponding areas with Masson's trichrome stain made many more capillary blood vessels obvious, some of which contained red blood cells, others appearing empty. The reticulin stain showed a layer of normal endothelial cells in these capillaries outside which was a layer of reticulin. It also showed a reticulin network around the individual tumour cells (Fig. 4).

(*b*) Zones rich in capillary blood vessels. Many of these were dilated and again a few were surrounded by two or more layers of tumour cells and the endothelial layer found to be normal. Using van Gieson's stain many of the capillaries had a prominent hyaline thickening in their walls—a point noted by Stout (1949) as being a characteristic of malignant haemangiopericytoma. Lying between these capillaries were varying numbers of cells with characteristics the same as those described above, these cells being separated from one another by varying amounts of collagen.

(*c*) Areas in which mature collagen was prominent forming wide bands (Fig. 3). A few tumour cells could be identified in the collagen. In places the collagen isolated small islands of tumour tissue.

(*d*) Round cell and plasma cell infiltration was present in all areas of the tumour.

(*e*) In some sections a number of smooth muscle fibres were identified.

It must be pointed out that careful searching revealed no mitoses in the tumour cells.

Sections from the paracervical nodules showed histological appearances similar to those already described in (*a*) and (*b*) above (Figs. 5 and 6). Bands of collagen were not present, though the tumour cells were separated in places by small amounts of collagen. The spindle-shaped cells present in these nodules stained as collagen with van Gieson and Masson stains. No smooth muscle fibres were present. Again, round cells and plasma cells were found to be infiltrating all areas. No mitoses were seen in the tumour cells.

Comment

The presenting symptom in this case was postmenopausal bleeding. Vaginal bleeding is stated to be a common mode of presentation for a haemangiopericytoma of the uterus. However, the bleeding in this case can be attributed to the polypoid hyperplasia of the endometrium alone. There did not appear to be any connexion between the endometrial polyps and the haemangiopericytoma of the uterus.

In addition to the primary tumour, the uterus contained a histologically proven fibroid—an association which has occurred in other cases described.

The primary tumour showed the presence of smooth muscle fibres whereas both paracervical nodules did not. It is possible that sections from further blocks of the paracervical nodules might have revealed smooth muscle, but on the other hand it could be that differentiation of the tumour cells had not gone so far as to form smooth muscle.

No mitoses were seen in any of the sections from the primary tumour or the secondary deposits. Pedowitz, Felmus and Grayzel (1954) state that the presence or absence of mitoses is not a good guide to the malignant nature or otherwise of the haemangiopericytoma. In the case described by them, which was clinically malignant, no mitoses were found. The only concrete evidence of malignancy is the finding of metastases.

It remains undecided whether the tumour cell of the haemangiopericytoma is the pericyte of the capillaries or is an undifferentiated mesenchymal cell producing many capillary blood vessels with their associated pericytes and smooth muscle fibres.

The patient is alive and well and shows no evidence of recurrence of the tumour eight months after operation. The follow-up period is admittedly short, but the prognosis for the uterine haemangiopericytoma is good. Hence the

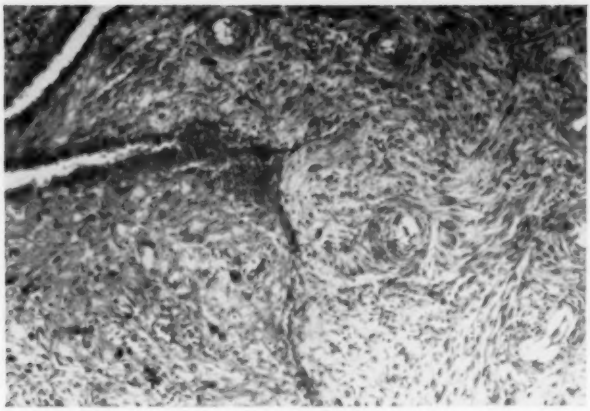

FIG. 1

Primary tumour. Round to spindle-shaped tumour cells and capillaries sheathed by several layers of tumour cells. H. & E. ×116.

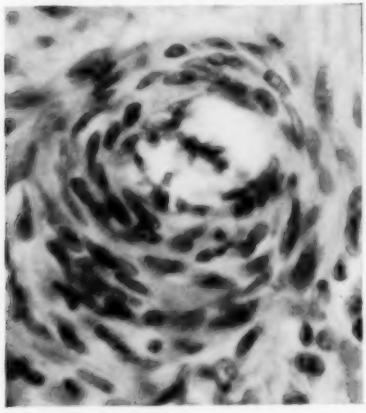

FIG. 2

Primary tumour. Capillary surrounded by many layers of tumour cells. H. & E. ×304.

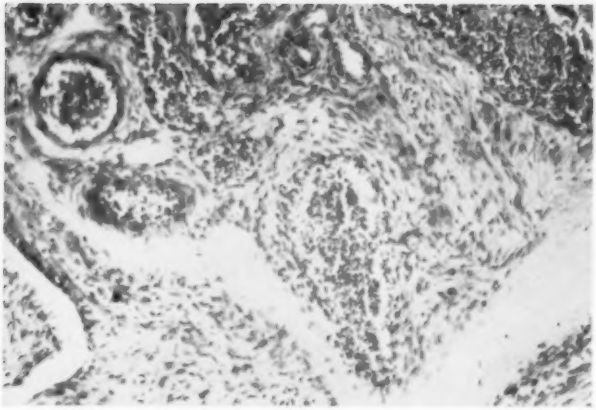

FIG. 3

Primary tumour. Several dilated capillaries and tumour cells. Band of collagen in the lower half of the picture. H. & E. ×116.

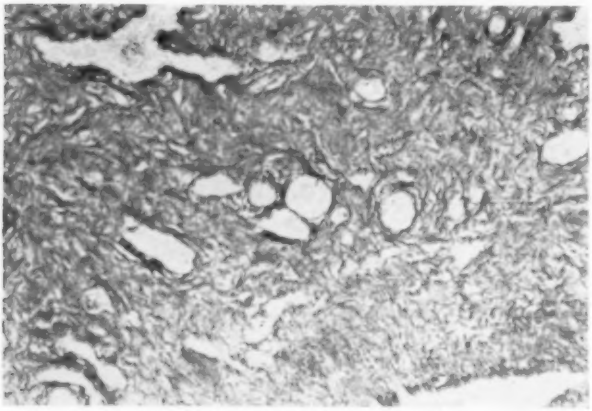

FIG. 4

Primary tumour. Several capillary vessels and individual tumour cells surrounded by reticulin. Reticulin stain ×116.

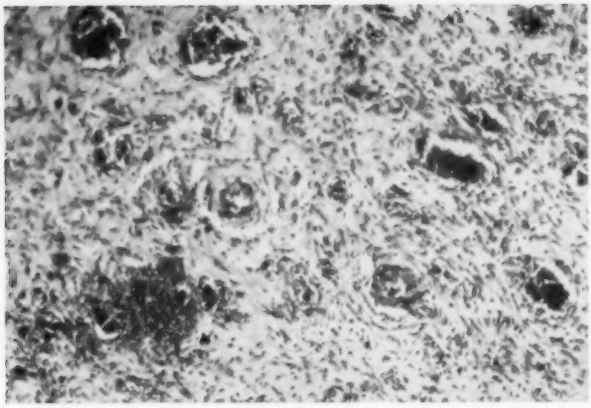

FIG. 5

Section from paracervical nodule showing many capillary vessels, tumour cells and collagen. H. & E. ×116.

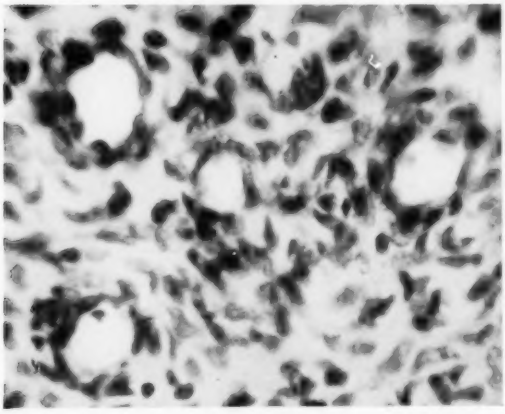

FIG. 6

Section from paracervical nodule. Tumour cells with round cell and plasma cell infiltration and capillaries which appear empty. H. & E. ×337.

importance of distinguishing this tumour—and this can only be done histologically—from the other uterine tumours with which it has been confused.

Acknowledgments

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PARAPLEGIA FROM FLEXION INJURY OF THE SPINE: A DANGER OF THE HIGH LITHOTOMY POSITION

BY

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DAMAGE to the cervical spine is a recognized hazard of manhandling the unconscious patient. In the general experience of anaesthetists and surgeons, it is very uncommon. In consequence, a fracture in the upper dorsal spine, resulting from the abrupt lifting of an unconscious patient into the high lithotomy position, and that complicated by paraplegia, appears to be worthy of mention.

CASE REPORT

The patient was an African woman aged about 40 years. She was admitted to hospital with a vesico-vaginal fistula. On 12th August, 1960, a vaginal examination was performed under anaesthetic. The following day she complained of pains across the upper chest and was noted to be having extremely severe extensor spasms of the trunk and lower limbs. She was placed, empirically, on cervical traction by a neck harness.

Full neurological examination seven days later revealed signs of an incomplete transection of the spinal cord in the upper thoracic region. The chest pains were, in fact, bilateral root pains in the fourth thoracic dermatomes. Below that level there was generalized hypo-algesia and hypo-aesthesia. Abdominal reflexes were absent, knee and ankle jerks were exaggerated and both plantar responses were extensor. Very severe hypertonia of the trunk and lower limbs, with periodic painful spasms, was a particular feature. Deep tenderness was noted over the second, third and fourth thoracic spinous processes.

Lumbar puncture was performed forthwith. Pressure was 60 mm. of water and there was a very sluggish rise on jugular compression and no fall on releasing that pressure. The cerebro-spinal fluid had no cells and protein content was 30 mg. per 100 ml. X-rays of the cervical spine were normal, but in the thoracic spine there was a recent and severe compression fracture of the body of the third thoracic vertebra.

Myelography was unavoidably delayed until 4th September, 1960, when complete block opposite the compression fracture was demonstrated.

There being no improvement in the physical signs whatever up to 15th September, laminectomy was performed on the following day. Laminae of the second, third and fourth thoracic vertebrae were removed to reveal a very poorly pulsating theca. This was opened and the cord was retracted gently to reveal a slight, diffuse posterior bulging of the anterior theca opposite the fractured vertebral body. It was decided that simple decompression should suffice: the theca was closed, covered with gelatin sponge and the wound sutured.

Recovery was prompt, with cessation of root pains and the severe spasms immediately after the operation. After four weeks the patient was starting to walk with assistance and steady improvement was maintained thereafter.

DISCUSSION

In this case there appeared to be very little doubt that the examination under anaesthetic

in the lithotomy position and the spinal injury stood as cause and effect. Radiologically the patient's spine was in no way porotic or otherwise abnormal.

Out of curiosity it was decided to test the effect of suddenly lifting the legs upwards from under the flexed knees in relaxed subjects lying supine with the neck extended. A jerking lift provoked sharp discomfort localized over the upper dorsal spine in three subjects. It was felt that it might be unwise to extend the experiment by fixing the neck in extension, as it would be during the manœuvre in the operating theatre; there the neck would be held in extension by the anaesthetist holding a mask over the face or holding the head itself if an endotracheal tube had been inserted.

The spine, as is so well known, tends to fracture near the junction of its fixed and mobile parts. Although the dorsal spine is rather rigid in the adult, its very rigidity is its liability. The last cervical and upper two thoracic vertebrae are relatively powerful bones whereas the next highest thoracic vertebrae are smaller and not as fixed by short, rigid ribs. Fractures in the upper dorsal spine are, in consequence, not at all uncommon.

As a result of this case, extreme care is advocated in lifting unconscious patients from the supine to the high lithotomy position. Any undue jerking movement or violence should be avoided while the anaesthetist might observe the movements of the upper spine with caution. A firm pillow placed lengthwise under the head, neck and inter-scapular region might be useful as an additional safety measure.

Summary

A case is described in which a picture of incomplete transection of the spinal cord, associated with a crush fracture of the third thoracic vertebra and with complete block on the myelogram at that level, followed examination under anaesthetic in the lithotomy position. Laminectomy and decompression was followed by a complete recovery of the cord.

The mechanism of the injury is discussed and certain simple precautions are suggested.

Acknowledgments

Appreciation is expressed to the Medical Superintendent, Mpilo Central Hospital, Bulawayo for permission to report this case.

ABERDEEN EXPERIENCE IN THE CYTOLOGICAL DETECTION OF UNSUSPECTED CARCINOMA OF THE CERVIX

BY

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IT is now accepted that cytological examination of the cervix can detect carcinoma at a very early stage and long before any clinical suspicion is aroused. What use should be made of this new method of diagnosis? There are formidable difficulties in applying the method on a large scale—shortage of trained technical staff, and difficulty of access to the community at large being perhaps the chief. Another difficulty is that the length of the pre-invasive stage of carcinoma of cervix is not known with any certainty, and probably varies widely from patient to patient. A negative smear may thus "guarantee" against cancer for as long as 10 years in some cases, but for a much shorter time in others. This factor determines the practicability or otherwise of using cytology periodically in any attempt to eliminate cancer of the cervix from a community.

If the great majority of cases have a pre-invasive stage which is close to the average in length (generally quoted as being about 10 years), periodic examinations would allow malignant changes in the structure of the cervical epithelium to be detected at a stage when the results of treatment would be excellent.

Should the pre-invasive stage be much shorter than the average of ten years in an appreciable number of cases examinations would have to be repeated too frequently to be practicable, at least on a large scale. Whatever the ultimate conclusion on these wide issues, our experience suggests that the method should be used as an aid to routine practice in all gynaecological departments. The teaching hospitals, at least, should have the resources to examine all women attending their gynaecological out-patient departments who are in the high risk categories. This paper describes the progress made in Aberdeen teaching hospitals during the first two years in which the method has been in use —from April, 1958 to March, 1960.

Smears are taken from the cervix and posterior vaginal fornix, using Ayre's spatula, from all parous patients over the age of twenty-five years, who attended the Gynaecological Department or the Postnatal Clinics. In addition several general practitioners, both in the city and country areas, have sent smears from their own patients. The smears are stained by Papanicolaou's method, and screened by one of us (F.C.), who reports on all smears which appear absolutely healthy. Doubtful or suspicious smears are passed to the other author (R.Y.) for final diagnosis.

Patients from whom a positive smear is obtained are admitted to hospital for further investigation. Smears are repeated, and if these confirm the previous findings, a wide "cone-biopsy" of the cervix is taken, and thoroughly examined histologically. Treatment depends on

TABLE I
Results

Age Group	<30 Years	30–39 Years	40–49 Years	50–59 Years	>60 Years	All
			Postnatal Patients			
No. of patients	658	648	36	—	—	1,342
Positives	2	7	—	—	—	9
"Pick-up rate"	0·3%	1·08%	—	—	—	0·6%
			Gynaecological Patients			
No. of patients	501	1,127	955	580	314	3,477
Positives	1	16	19	3	2	41
"Pick-up rate"	0·2%	1·4%	1·9%	0·52%	0·63%	1·2%
Total number of patients						4,819
Unsuspected positive smears						50
"Pick-up rate"						1·04%
Histological diagnosis by biopsy of cervix:						
Intra-epithelial carcinoma						34
Early invasive squamous carcinoma						16

the histological findings, radiotherapy for the invasive, and usually hysterectomy for the intra-epithelial lesions.

RESULTS

During the two years under review, 4,819 patients had cytological smears taken from the cervix and vagina, yielding 50 positives. In none of these patients did the symptoms or the findings at clinical examination lead the gynaecologist to suspect carcinoma of the cervix. This yield or "Pick-up Rate" of 1·04 per cent agrees with those of most other workers (Anderson, 1959). These cases are set out more fully in Table I.

The Effect of Age and Parity on the "Pick-up Rate"

With the number of cases under review it is not possible to separate the effects of age and parity.

Table I shows that the highest incidence (1·9 per cent) occurred in the age group 40–49 and that there is a sharp falling off in the age group 50–59 to about one-quarter of that in the age group 40–49. Under the age of 30 the incidence of positive smears is very low. Age for age the results from the Postnatal Clinics in the City are very similar to those from the Gynaecological Department, but since there were very few women over 40 years of age and a greater proportion under 30, the overall rate of positive smears is much less.

The average age of the patients with intra-epithelial cancer was 38 years and of those with invasive cancer, 43 years. The age difference between the two groups of only 5 years is about half that usually reported (Carter *et al.*, 1956, 10 years; Anderson, 1959, 12 years). No fewer than 6 of the 16 patients with invasive lesions were less than 35 years of age, which seems an unusually high proportion of young women.

While the parous woman has a greater chance than the nullipara of developing cervical cancer, the risks do not appear to be directly proportional to the number of children. The fact that women with cancer have on average more children than those who do not may be due to the fact that they marry younger and have more time in which to have children. The rate of childbearing is not greater than in comparable non-cancerous patients (Lawson, 1957). In this series the average parity (including abortions)

was 3·7, and, of the 49 patients who had borne children, 40 were less than 25 years of age at the time of the first pregnancy, and 15 of these were less than 20 years old. It may be that the interval of time between the birth of the first child and the age of 50, the end of the most susceptible age period, may be the most significant feature influencing the incidence of a positive smear or invasive cancer.

The problem of the effect of age and parity is further complicated by the fact that there is a well-marked social gradient in the death rate from cancer of the cervix and presumably also in the incidence of the disease.

The higher incidence in women in the lower social classes might be due to the fact that they marry earlier and have more children than those in the upper social classes. They therefore have a longer period of exposure before the age of 50 to the conditions predisposing to cancer of the cervix. Other possible predisposing factors may be a lower level of nutrition and poorer hygiene. According to Kottmeier (1959) the rising standard of living in Sweden has not resulted in a decrease in the incidence of cancer in the lower social classes. He thinks that if anything the reverse is true. On the other hand, since 1945 women are marrying at a much earlier age and this may be of some significance by increasing the length of the high risk period.

The discovery of 16 cases of unsuspected early invasive cancer in 2 years emphasizes the value of the method. The fact that the smear technique prevents serious mistakes in diagnosis and treatment is illustrated by the two following cases.

Case 1

Mrs. H.F., age 28 years, para-5 (including 3 abortions).

This patient was referred to the Gynaecological Out-Patient Department, with a complaint of excessive but regular periods; there was no intermenstrual bleeding or vaginal discharge. Pelvic examination revealed no abnormality, and the cervix appeared perfectly healthy. A routine smear from the cervix revealed many malignant squamous cells, and biopsy revealed an early invasive carcinoma. Full radium therapy was given, and the prognosis is likely to be excellent.

Case 2

Mrs. L.C., age 31 years, para-4.

This patient was admitted to the Gynaecological Department for dilatation of the cervix and curettage because of dysmenorrhoea. Pelvic examination again revealed no abnormality, and the cervix seemed healthy. However, a routine smear taken from the cervix, on admission, showed malignant squamous cells. Cone biopsy of the cervix showed an invasive carcinoma. Full radium therapy was given with an excellent prognosis.

In both of these young women invasive carcinoma of the cervix would have remained undetected but for routine cytology. In neither case was biopsy of the cervix indicated before the result of the cytology was known. The importance of this early diagnosis need hardly be stressed.

Treatment

The 50 patients reported in this series are all alive and well at the time of writing, the interval after treatment varying from 30 to 6 months. Of the 16 patients with invasive squamous carcinoma, 15 were treated by radium and radiotherapy alone, and one by radium followed by a Wertheim hysterectomy. Treatment of the intra-epithelial lesions consisted of abdominal total hysterectomy in 28 cases, vaginal hysterectomy in 2, Manchester repair operation (amputating the cervix at a high level) in 1, radiotherapy in 1, and extensive cone biopsy of cervix only in two patients, who refused hysterectomy. Smears taken from these latter patients (as from all others) at three-monthly intervals have been consistently negative. Of the 30 hysterectomy specimens available for complete histological examination, only 12 had residual intra-epithelial cancer present, and in no case was there evidence of invasive growth.

Discussion

With regard to the technique of taking smears, the vast majority submitted to us have been satisfactory. We have no doubt, however, that the cervical scrape is much superior to the vaginal aspiration smear; this agrees with Ullery and Hollenbeck (1958) who reported 18 unsuspected cervical carcinomas in which the aspiration smear was negative and the cervical scrape positive, and with Cuyler *et al.* (1952). The cervical scrape may be more inconvenient to obtain, but its greater reliability makes it the method of choice.

"Cancer *in situ*" may not invariably progress to invasive cancer but all the indications suggest that this happens in a high proportion of cases. In 16 of our 50 cases with a positive smear and no clinical signs or symptoms of cancer, penetration of the basement membrane of the epithelium had already occurred. In many, sections of the cervix showed all variations in histological appearance from the normal epithelium to invasive cancer. Kottmeier (1955) reported 23 cases in which intra-epithelial growths had been treated expectantly, with subsequent development of invasive cancer.

The value of this method of diagnosis therefore seems undisputed and it should be available to all gynaecological clinics. Given the necessary technical help the methods could easily be used in all vulnerable women admitted to general surgical and medical hospital wards. We find that this is now providing an additional 200 patients per months who are over the age of 30 and parous. We have found such patients most co-operative despite the fact that many have no gynaecological complaints. Consequently we have been encouraged to consider extending the scheme to the population at large. This is more difficult however and requires the co-operation of the family doctor and a careful study of methods of approach to women not receiving any medical care or treatment at the time. The uncertainty about the variations in the life history of the pre-cancerous lesion which remains complicates the problem of the approach to the "well" patient. Despite these difficulties we are inclined to agree with Way (1955) that early diagnosis in the pre-invasive phase before bleeding and other signs develop will do much more to lower the death rate from cancer of the cervix than advances in treatment of clinically diagnosed lesions by either surgery or radiotherapy.

Summary

An account is given of two years' experience of cervical cytology in Aberdeen. Smears were taken from 4,819 patients in the Gynaecological Department, the Postnatal Clinics and general practice, These yielding 50 unsuspected positive smears, a "Pick-up Rate" of 1·04 per cent. These 50 patients were investigated by cone-biopsy of the cervix: in 34 patients an intra-epithelial carcinoma was found, and in the remaining 16 there was an early invasive squamous carcinoma. A plea is made for the widespread extension of the method.

Acknowledgments

We wish to thank all the very many people who have co-operated with us by taking smears from their patients. Without their help, the cytology service could not have been established. Thanks are especially due to Professor Sir Dugald Baird for his continuous encouragement to us, and for the provision in his department of the facilities by which the service is carried on.

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HISTOCHEMICAL CHANGE IN ENDOMETRIUM

Normal Endometrium

BY

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"PHYSIOLOGICAL histochemistry has as its chief aim the morphological localization within tissues of the chemical components which are involved in physiological processes and the correlation of any changes in this chemical machinery with the different functional states of the tissues or organism" (Dempsey and Wislocki, 1946).

Since some three to four thousand histological specimens of endometrium are examined annually in the pathological department of this hospital, it was decided to investigate the pattern of histochemical change occurring in this tissue. Before attempting an analysis of the many pathological conditions, it is necessary to have as complete an understanding as possible of the normal events which take place. This investigation was carried out as part of a larger study (Barbour, 1958).

Specimens were selected from the endometria of patients whose menstrual histories were normal and whose clinical conditions were in no way related to any upset of that function. Only specimens showing whole thickness of intact endometrium were used. Additional sections were cut from the paraffin blocks and these were stained differentially whereby accurate comparisons of components could be made at identical sites in the tissue and at all phases of the menstrual cycle. The chemical substances which were investigated are given under the heading of the stain employed for their detection.

In this way a large number of specimens was examined but, since the description is qualitative and the results are known to be uniform, there is no necessity to quote figures. In the account of the findings which follows opportunity is taken to review the literature in relation to the component under discussion.

PERIODIC ACID-SCHIFF
(McManus, 1946)

Many substances give a positive reaction when stained by this method but, of these, the substances reasonably thought to be associated with endometrium may be compound lipids, glycogen and mucus. The P.A.S. technique is commonly used for exhibiting mucins as a method by itself and the lipid and glycogen fractions can be differentiated by other methods which will be described later.

The positive material is present, as granules, in the superficial cytoplasm of gland cells in the proliferative phase and becomes more intense in the early secretory phase but the outstanding feature of this time is the large amount of material in the gland lumen. The stromal cells show a fairly uniform positive reaction in the proliferative phase especially the cytoplasm of the spindle cells. In the secretory phase, large areas of ground substance take up the dye in the vicinity of gland convolutions. The cytoplasm of the surface epithelial cells shows a positive reaction in the proliferative phase. This becomes more intense at the time of ovulation.

This method may be assumed to have shown the abundant production of mucins in normal endometrium but it is also possible to demonstrate the presence of glycogen and fats by other stains.

Best's Carmine Technique

This test is specific for glycogen and is determined by staining control sections after diastase digestion. The absence of stained material, following enzyme digestion which was previously carmine positive, is proof that the substance is glycogen.

Glycogen first appears, to any extent, in the gland cells at the time of ovulation and is predominantly basal in position. In the established secretory phase, the strongest glycogen reaction is seen in the cytoplasm of the cells of the surface epithelium and of the glands. It is mostly present in the basal cytoplasm of these cells but may extend beyond the nuclei to the superficial cytoplasm. Where this occurs, the glycogen persists either as globules or as minute granules. In the glands, these may be extruded into the lumen. Small granules can also be seen in the areolar spaces of the stroma.

According to Vesterdal-Jørgensen (1950) large amounts of glycogen are always demonstrable in the normal secretory phase but cannot be said to be specific because it is present at any stage of the cycle even if it is but inconstantly present in the menstrual and proliferative phases. McKay *et al.* (1956) found that most of the biochemical alterations were due to changes in the glandular and surface epithelium whereas the stroma contributes only slightly. Glycogen content was low in the proliferative phase and increases in the secretory phase. Dezza (1955) found very little glycogen in the proliferative phase but conspicuous quantities in the progestational phase. The findings of the present study would appear to be in accord with these statements.

Rossmann (1940) is inclined to regard glycogen as a simple nutriment and as an indicator of a disproportion between intake and consumption or of reduced oxidation analogous to the evaluation of the substance in other localities. The source of glycogen is glucose carried to the region by the blood stream. Synthesis of the glycogen is accomplished from a hexose-phosphate which is split by alkaline phosphatase. Hisaw and Greep (1938) have shown that glycogen is retained basally in the cells in cases of prolonged oestrin administration and only small amounts of glycogen are carried to the lumina of the glands. When progesterone was given, there was increased elimination of glycogen. Ferin (1947) found that, in ovariectomized subjects to whom folliculin had previously been given, a single dose of progesterone, administered intramuscularly, produced basal vacuole formation in the endometrium within 24 hours. Glycogen was found first as fine granules in the surface epithelium and in the necks of the glands. Within a few hours granules were also found in the depths of the glands. Falconer (1948) concludes that an incomplete stromal cell reaction indicates that the storage of glycogen is insufficient. Finally, de Senarclens (1949) investigated the time of appearance, during the menstrual cycle, of glycogen and mucus in the endometrial glands. The biopsy specimens were correlated with ovarian changes. Glycogen was present in small amounts on the 6th day of the cycle. It appeared in large amounts on the two days following ovulation and this coincided with the appearance of mucus. The presence of large amounts of glycogen and mucus indicated progesterone action. The progesterone may be extragenital, for example, from the adrenal, or it may originate from the theca interna cells which sometimes undergo an epithelioid instead of a fibroblastic reaction.

Sudan Black

According to Dempsey and Wislocki (1946) Sudan Black makes fat more visible than Sudan Red and this method was employed in the present study. During the proliferative phase, the superficial cytoplasm of the cells of the glandular epithelium showed the presence of fat droplets. Fat secretion appeared in the gland lumen in the early secretory phase and the quantity increased as the phase progressed. Premenstrual endometrium appeared to be empty of fat. At all stages there was a greyness of the stromal cytoplasm. The dark-stained material in the lumen appeared to correspond in position to the P.A.S. positive substance.

Gillmann (1940) studied fat changes in endometrium. Staining with Scharlach does not show any fats in the glands during the proliferative phase whereas there are a few droplets situated

at the poles of the nuclei in the stromal cells. In the progesterone phase a remarkable accumulation of fats is seen in the basal third to one-half of the glandular cells below the nuclei. This is believed to denote an optimal lutein effect. By excessive dosage of oestrogens, associated with a deficiency of progesterone, an abundance of fat is seen in the stroma while the glands are empty.

The findings of the present study, even although a different stain were used, do not correspond with those of Gillmann. It has been observed that fine fat droplets may occur in the cytoplasm of stromal cells at all stages of the cycle, otherwise fine droplets were seen only in the superficial cytoplasm of the gland cells until the secretory phase was reached. Thereafter, the intense stain of the secretion in the lumen was noticed to increase in quantity to the immediate premenstrual phase. At menstruation the endometrium and gland lumina were devoid of fat-staining substance.

Methyl-green Pyronin

Basophile substance in endometrium, presumably identical with ribonucleic acid, has been studied by Dempsey and Wislocki (1945, a and b). Nucleic acids are abundant in cells in which rapid protein synthesis is taking place in the production of the main bulk of cytoplasmic protein for growth or for secretion. In such cells, ribonucleic acid is particularly abundant in the cytoplasm which is intensely basophilic and the nucleolus is also large and prominent (Davidson, 1953).

In the course of this study sections were stained by the methyl-green pyronin (M.G.P.) method and also control sections were treated with ribonuclease. The ribonuclease treated section was compared with the M.G.P. stain and the absence of a structure which was present in the M.G.P. slide indicated that this structure was composed of ribonucleic acid (Fig. 1). In the early proliferative phase, ribonucleic acid is present throughout the cytoplasm of the surface epithelial cell. In the gland cells the substance is seen basally and on the upper pole of the nucleus. The stromal reaction is fainter and granular. In the late proliferative phase the cytoplasm of the surface epithelium stains more intensely. The gland cell shows a similar reaction but now the entire cytoplasm stains evenly. The granular stromal reaction is more distinct. In the early secretory phase it was noted that the spindle stromal cell cytoplasm retained some staining properties despite treatment with ribonuclease. As the secretory phase progresses, the gland cell cytoplasm stains superficially to the nucleus, becomes paler and abundant stained secretion is present in the lumen.

Atkinson *et al.* (1949) state that the ribonucleic acid content of the cytoplasm of cells provides an index of the rate of protein synthesis. The findings of the present study appear to correspond with their description although these authors make no mention of the activity of the stroma. It would appear that there is a morphological difference in the cytoplasm of the spindle stromal cell and that a substance other than ribonucleic acid is retained after treatment with ribonuclease. Comparison of the M.G.P. sections with those stained P.A.S. shows that the volume of material secreted contains ribonucleic acid in addition to other materials unaffected by ribonuclease.

McKay *et al.* (1956) report that ribonucleoprotein is present in increasing amounts reaching a peak in the late proliferative phase and decreasing in the progestational phase. They also observe that most of the biochemical alterations were due to changes in the glandular and surface epithelium whereas the stroma and blood vessels contributed only slightly.

Alkaline Phosphatase

In order to conduct this investigation it is not possible, for chemical reasons, to use formol-corrosive fixed sections of endometrium as heretofore. Gomori introduced a technique whereby the enzyme is identified by its action on a substrate containing organic phosphate, in the presence of calcium ions, to form calcium phosphate *in situ*. The calcium phosphate so formed may then be directly demonstrated by treating with cobalt nitrate and ammonium sulphide. Fresh endometrium was fixed in cold acetone.

In the early proliferative phase, alkaline

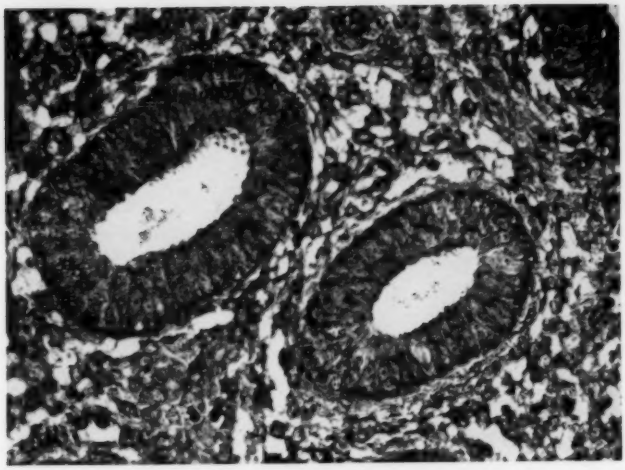

FIG. 1a
Proliferative endometrium stained M.G.P. ×350.

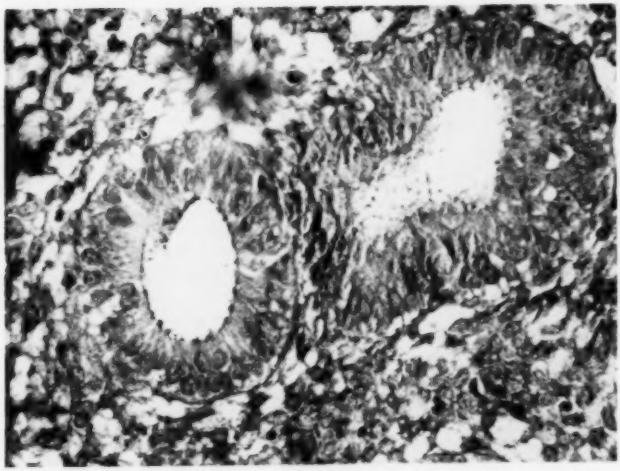

FIG. 1b
Proliferative endometrium stained M.G.P. after treatment with ribonuclease. ×350.

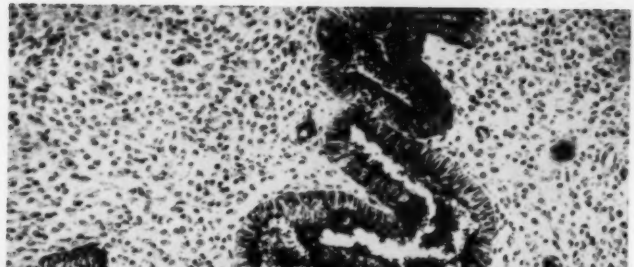

FIG. 2a
Late proliferative phase. ×135.

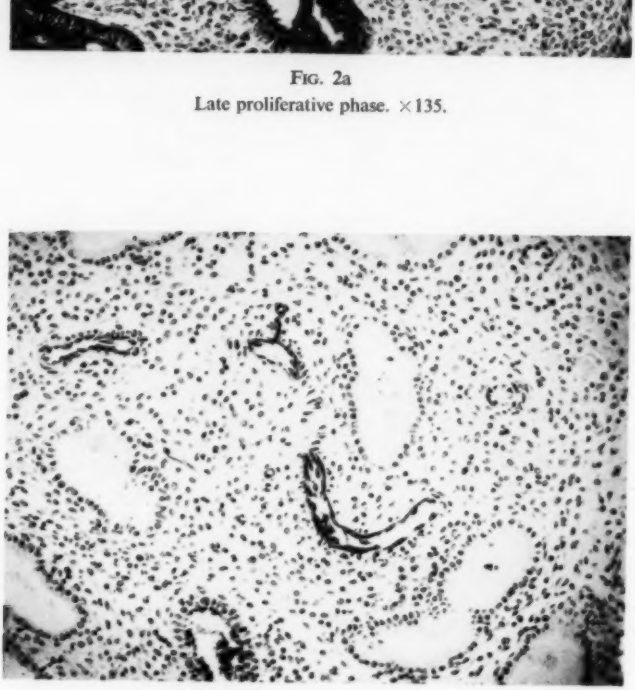

FIG. 2b
Late secretory phase. ×135.
Alkaline phosphatase.

phosphatase was present in the entire cytoplasm of the gland cells and the surface epithelium cells. The staining became more intense in the late proliferative phase. In the early secretory phase, it was found in the superficial cytoplasm of the gland and surface epithelial cells, in the gland lumina as an irregular amorphous mass and also lining the blood vessels. In the late secretory and premenstrual stage, alkaline phosphatase could be found only in the blood vessel walls. The stroma did not appear to share in this activity at any stage (Fig. 2).

The findings of Botella Llusia (1956) are similar and he makes the further observation that the secretory phase is characterized by depletion of alkaline phosphatase in the glands, its deposit in their lumina and its presence in the vessel walls. If none is observed in the 24th–26th days of the cycle in the vessels, it is inferred that ovulation has not occurred. Hedberg (1950) states that phosphatases are enzymes capable of hydrolysing phosphoric esters and that phosphatase activity is determined by oestrogenic influence. Since the folliculin secretion curve, judged by urinary excretion, has a second peak in the second half of the secretory phase, the decrease in phosphatase activity in this phase is attributed to the inhibitory effect of progesterone. It is suggested that there is a functional relation between phosphatase activity and proliferation. Atkinson and Engle (1947) showed, in the ovariectomized monkey, that the administration of oestrogens is associated with the formation of alkaline phosphatase and that if progesterone is then given, the amount of the enzyme is decreased. Besides taking part in glycogen metabolism, alkaline phosphatase is concerned in the metabolism of nucleoproteins which indicates protein synthesis during the period of growth stimulation of the uterine glands.

Metachromasia

Certain tissue components in the presence of certain dyes of the coal-tar group will stain a colour other than the basic colour of the dye. In the present study, during the early proliferative phase, a contrasting reddish-violet substance was noted throughout the cytoplasm of the surface epithelium cell. This substance had a granular appearance in the superficial cytoplasm of the gland cell but stained intensely in the areas just superficial and basal to the nucleus. The cytoplasm of the round stromal cell also showed granular staining. During the proliferative phase the substance moved to the superficial cytoplasm of the surface epithelium, became granular throughout the whole cytoplasm of the gland cell and maintained its granular appearance in the stromal cytoplasm. In the transitional phase, the substance appeared as droplets in the superficial cytoplasm of the surface epithelium and, similarly, in the gland cell. The subnuclear vacuole of the gland cell had a few minute stained granules adhering to its surface. The stromal cytoplasm showed granular staining. During the secretory phase, droplets were seen in the superficial cytoplasm of the surface epithelial and gland cells. The gland lumen was partly filled with a pink staining amorphous secretion. The intercellular stromal substance stained in a granular fashion. In the premenstrual phase, the surface epithelial and gland cells appeared to be devoid of the stained material. A small residue of secretion may be present in the gland lumen. There are droplets in the cytoplasm of the decidua-like stromal cells. The intercellular substance of the stroma also showed droplets.

These findings seem to be at variance with those of Vesterdal-Jørgensen (1950) who states that metachromasia is never seen in the glands in the early phase of proliferation. During the latter part of the proliferative phase accumulations of secretion are in evidence in the basal part of certain of the cells of the surface and at the necks of the glands. These accumulations increase in the transitional phase when the secretion occupies the vacuoles below the nuclei which are visible in preparations stained by the ordinary routine methods (that is, the metachromatic substances are found in the same localities as are the lipids and glycogen). In the secretory phase, the gland cells are filled with the secretion, at first, basally; later, the secretion is present throughout the cell to its apex and is then discharged into the lumen some days before the onset of menstruation. Thus, premenstrually and menstrually, the glands are empty whilst the

secretion is piled up in the lumina or may, occasionally, be absent. He found that the method exhibited vagaries in the staining results. However, in the present study, the results as given have shown a constancy throughout the great number of specimens examined. Where metachromatic sections have been compared with identical sections stained P.A.S., Best's Carmine, M.G.P. and Sudan Black, it is seen that metachromatic substance is sited in those localities in endometrium where mucin, glycogen, ribonucleic acid and lipids are detected.

Vesterdal-Jørgensen (1950) concludes from a comparative table of reaction results that the substance demonstrated is a mucopolysaccharide present in the cell before discharge into the lumen. Davidson (1953) quotes Lison and Matsaars (1950) when stating that metachromatic staining is usually due either to the presence of the sulphuric esters of polymeric carbohydrates or to polyphosphates of the hexametaphosphate type. McKay (1950) demonstrated intercellular stromal metachromasia during the proliferative phase. It was diminished or absent during the early secretory phase and re-appeared between the pre-decidual cells in the late stages of secretion. There appeared to be a reciprocal relation between intercellular stromal metachromasia and oedema of the stroma. Mast cells were present during the proliferative phase; they were fewer in number or disappeared in the early stages of secretion and re-appeared in moderate numbers in later stages. Metachromatic granules, which were probably of a ribonucleoprotein nature, occurred in pre-decidual cells of the late secretory endometrium. He suggests that the secretion of the proliferative phase contains ribonucleoprotein but, during the secretory phase, mucus is an additional constituent.

Stromal Supporting Tissue—Collagen Fibres

In the course of the main study, comparative sections were stained by Van Gieson's method in order to show the presence of collagen fibres in stromal ground substance. Collagen was found at all stages of the menstrual cycle as a fine open fibrillary network in interglandular spaces, adjacent to gland cells and also around the endometrial capillaries. Where gland cells were enshrouded by spindle stromal cells, the cytoplasm of these spindle cells gave a typical collagen stain.

These were the main methods of histochemical comparison employed but it may be of interest to give the findings of two further experiments which were made.

Frozen Sections Stained by Sudan III

The object of this investigation was to assess the reliability of the Sudan Black method. Fresh frozen sections were employed thereby preventing simultaneous comparison by reason of the method of fixation. The results, however, showed that fat substance appeared to be absent in the proliferative phase, appeared in the superficial cytoplasm of the gland cells in the transitional and secretory phases with increasing amounts in the gland lumina until the point of menstruation. Minute histology is extremely difficult with frozen sections but the impression gained was that the subnuclear vacuoles of the gland cells of the transitional phase did not contain fatty substance.

Secretory Granules

Maximow and Bloom (1953) depict the first stage in the elaboration of secretion granules in the pelvic gland of the mollusc *Triton taeniatus*. The method employed was fixation of tissue in Champy fluid and staining by Altman's method and aurantia. This was tried on selected specimens of endometrium but close examination failed to provide a convincing demonstration of similar secretory granules in the gland cells.

Summary

A brief description of the physiological histochemical change taking place in normal endometrium has been given. This has been correlated with a review of the literature. There has been no attempt to compare the histological findings of this study with the biochemistry of ovarian hormones. Being mindful of the criteria by which the investigation was conducted, it is reasonable to assume that, since the menstrual

histories of the subjects from whom the specimens were obtained were normal and, further, since the histological pattern as shown by ordinary routine staining was also normal, therefore, the levels of oestrogen and progesterone must also have been normal. It would not be practicable to include extensive photographic records of the histochemical changes at each phase of the menstrual cycle and I have confined the illustrations, here, to the identification of ribonucleic acid and alkaline phosphatase where the contrast of these stains should be suitable for black and white reproduction.

In conclusion, I would like to express my sincere thanks to Mr. Thomas Pearston and Mr. Edward Macpherson, the Chief and Senior Laboratory Technicians at this hospital, for their unfailing skill and energy in the preparation of the material and, also, to the former for making the photomicrographs.

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THE SIGNIFICANCE OF ATYPICAL ENDOMETRIAL HYPERPLASIA

BY

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ATYPICAL endometrial hyperplasia (Novak and Rutledge, 1948) is quite distinct from ordinary benign hyperplasia and often it is difficult to separate certain forms from a frankly malignant lesion. Novak (Novak and Rutledge, 1948; Novak and Novak, 1958) undoubtedly regarded the milder lesions as benign but appears to have thought removal of the uterus to be the proper treatment in the more advanced cases. Te Linde, Jones and Galvin (1953) consider that many cases diagnosed as atypical hyperplasia are, in fact, carcinomata. Hertig, Sommers and Bengloff (1949) are of the opinion that such epithelial proliferations suggest a pre-cancerous state and have applied the term "carcinoma *in situ*" of the endometrium. Speert (1952), Arfwedson and Winblad (1953) and Bamforth (1956) are of much the same opinion about the tendency of some lesions to become invasive carcinoma. So far, however, not sufficient data are available for a definite attitude regarding prognosis in the individual case of atypical hyperplasia. Nor has much been written about the relation between the more obviously benign and the doubtfully malignant forms of the lesion or about the likelihood of the former becoming malignant.

In the present paper an attempt has been made to classify the lesions into three grades, basing the distinction on the degree of the atypical features. In this way it is hoped to clarify the position regarding the pre-cancerous nature of the lesion and to indicate more accurately the probability of the development of a carcinoma in a particular case.

CRITERIA FOR THE DIAGNOSIS OF ATYPICAL HYPERPLASIA

Atypical hyperplasia of the endometrium is distinguished from simple hyperplasia by some or all of the following features:

(1) Increase in the number of glandular structures (Fig. 1) often with considerable reduction in the amount of stroma between them (Fig. 2, top).
(2) Increase in the amount of cytoplasm relative to the nucleus in the epithelial cells (Fig. 3).
(3) Increase in the size of the nucleus with a tendency to rounding (Fig. 4).
(4) Irregularity in the size of the glands (Fig. 5).
(5) Complexity of glandular patterns due either to decrease in the intervening stroma or to intra-luminal tufting of the epithelium (see Fig. 2).
(6) Stratification of the epithelial cells (Figs. 6, 7).
(7) Eosinophilia or lilac-staining of the cytoplasm.
(8) Vacuolation of the cytoplasm (see Fig. 4).

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FIG. 1
Atypical hyperplasia Type 2.
The condition is recognized here mainly by the abnormal number of glandular structures. ×17.

FIG. 2
Atypical hyperplasia.
The one at the top, Type 3, and at the bottom, Type 1. ×17.

FIG. 3
Atypical hyperplasia Type 2.
Near the top is a gland of ordinary proliferative type. The atypical glands contain cells with more abundant cytoplasm. ×68.

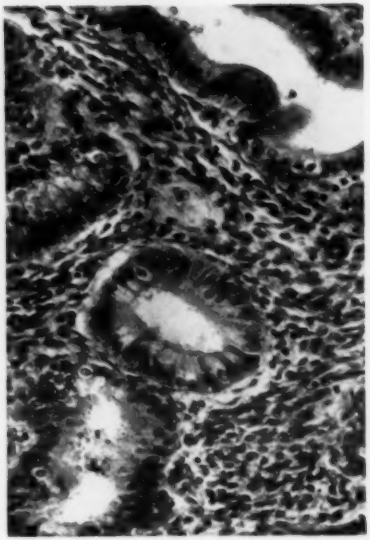

FIG. 4

Showing greater detail of the cells in one of the glands shown in Figure 3. There is greater increase in the amount of cytoplasm than in nuclear material. ×274.

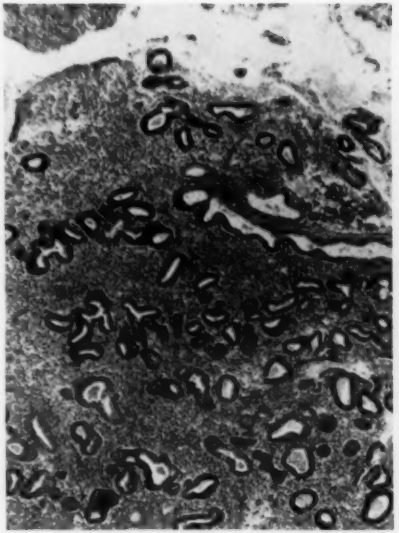

FIG. 5

Atypical hyperplasia Type 2.

The glands are increased in number and have larger constituent cells than normal. ×17.

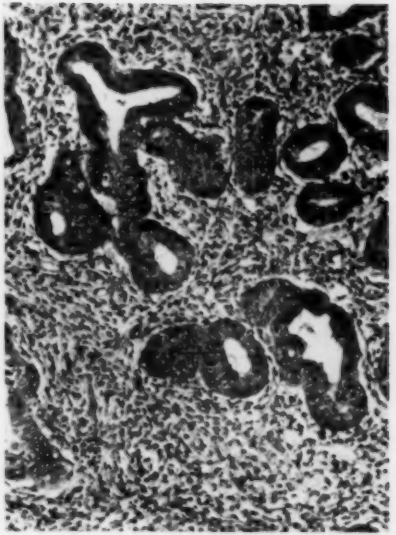

FIG. 6

Showing greater detail of the glands from the same case as Figure 5. ×68.

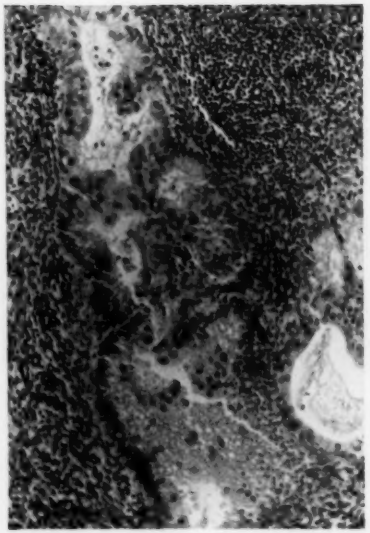

FIG. 7

Atypical hyperplasia Type 3.

Showing details of stratified epithelial cells. Large areas of this type of lesion are readily mistaken for carcinoma. ×68.

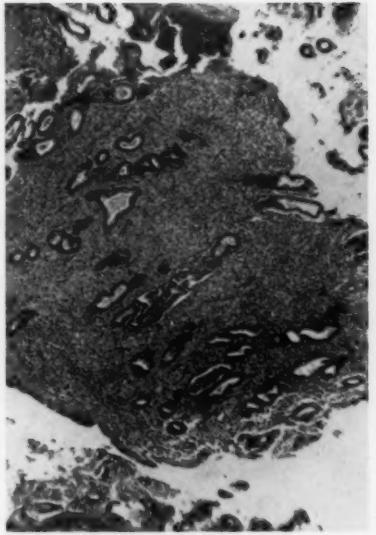

FIG. 8

Atypical hyperplasia Type 1.

The glands in the upper half of the particle are atypical. Three sections through a normal proliferative gland are seen in the lower end. ×17.

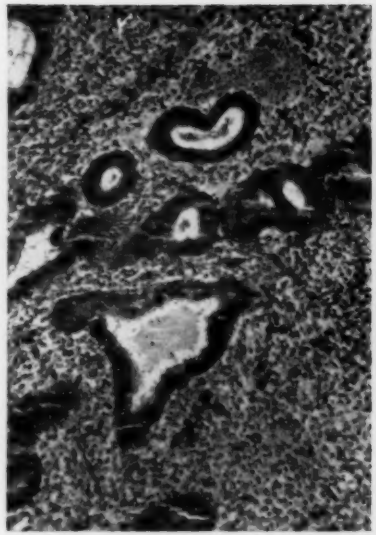

FIG. 9

Showing greater detail of the structure of the glands in Figure 8. ×68.

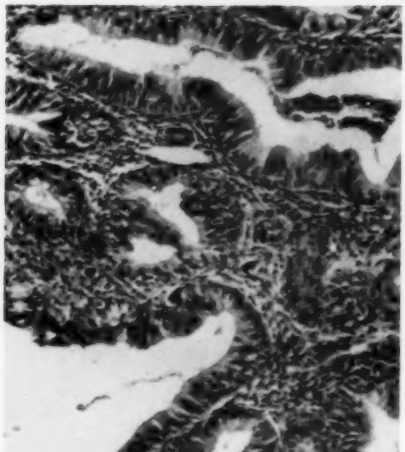

FIG. 10

Showing glandular proliferations of complex structure with very little intervening stroma. Atypical hyperplasia Type 3 of somewhat carcinomatous appearance. ×68.

Classification of the Degree of Atypical Hyperplasia

An arbitrary division into three types of atypical hyperplasia has been made in order to assess the prognostic significance of the appearances in a particular case.

Type 1. Cases showing some of the above features in mild form together with ordinary hyperplasia (Figs. 8, 9).

Type 2. Cases easily separated from ordinary hyperplasia without changes suspicious of malignancy (Figs. 1, 3, 4, 6).

Type 3. Cases of atypical hyperplasia only just distinguishable from carcinoma (Figs. 2, 7, 10).

Material

There were 257 cases diagnosed as atypical hyperplasia at the Royal Women's Hospital, Melbourne, in the 20-year period 1939–1958. Subsequent records of 95 of these were not available. One hundred and twenty-eight of the remaining 162 cases were selected for consideration, the remaining 34 cases being excluded because the authors considered the hyperplasia in them was not atypical or had actually become early carcinoma.

The 128 cases selected include 78 hospital cases and 50 private cases. The private cases selected were those treated by hysterectomy with or without prior curettage. Forty-three of the hospital cases had hysterectomy subsequent to one or more curettages.

Sections were examined by both authors independently and were graded as representing one of the three types of atypical hyperplasia as defined above. As far as was possible, slides showing carcinoma in those cases with co-existing tumours were not examined at the time of assigning the degree of hyperplasia.

Age Incidence

The average age of patients was 50 years with a range between 24 years and 76 years. The greatest number occurred in the 40–49 years group. Two of the patients who subsequently were found to have carcinoma were 24 and 27 years of age at the time of the initial diagnosis of atypical hyperplasia. In the first, carcinoma was found 9 years later and in the second, 7 years later. Both were grossly obese.

Symptoms

The main symptoms were irregular or continuous bleeding or excessive menstrual loss. Thirty-five per cent of the patients with abnormal bleeding were post-menopausal. Eight per cent of the patients complained of dysmenorrhoea as the main symptom and 7 per cent of vaginal discharge.

Findings

The incidence of carcinoma at the time of the original diagnosis of atypical hyperplasia or occurring some months or years later following curettage together with the incidence of the three types of atypical hyperplasia is shown in Table I.

Table I

Atypical Hyperplasia and Associated Carcinoma

Atypical Hyperplasia	Number of Cases	Number with Carcinoma	Percentage with Carcinoma
Type 1 ..	26	4	15
Type 2 ..	62	15	24
Type 3 ..	40	18	45
Total ..	128	37	29

The 128 cases may be grouped as follows:

(1) The progress of 60 cases diagnosed as atypical hyperplasia from scrapings and later treated by hysterectomy is shown in Tables II, III and IV.

(2) A further 12 cases in which atypical hyperplasia was initially diagnosed on curettage were subsequently found to have endometrial carcinoma. The details of these cases are set out in Table V.

(3) Another 21 cases diagnosed from curettings did not have subsequent hysterectomy. Eleven of these were not followed. The

TABLE II

Type 1 Atypical Hyperplasia

Progress of Atypical Hyperplasia	Interval to Hysterectomy			
	Cases			
	3 Months	3 Months to 1 Year	1 to 3 Years	3 Years
No evidence	8	2	1	1
Unchanged	3	–	1	–
Less severe type	–	–	–	–
More severe type	5	1	1	–

TABLE III

Type 2 Atypical Hyperplasia

Progress of Atypical Hyperplasia	Interval to Hysterectomy			
	Cases			
	3 Months	3 Months to 1 Year	1 to 3 Years	3 Years
No evidence	3	4	1	–
Unchanged	6	1	1	1
Less severe type	7	2	–	1
More severe type	2	1	1	–

TABLE IV

Type 3 Atypical Hyperplasia

Progress of Atypical Hyperplasia	Interval to Hysterectomy			
	Cases			
	3 Months	3 Months to 1 Year	1 to 3 Years	3 Years
No evidence	–	–	–	–
Unchanged	1	–	–	–
Less severe type	3	2	–	–
More severe type	–	–	–	–

TABLE V

Cases of Atypical Hyperplasia and Subsequent Carcinoma

Case	Age	Parity	Symptoms	Curettings	Subsequent Tissue	Interval
40	24	Nullipara	Pain and vaginal discharge. Obesity	Type 1	Uterus (Ca)	9 years
66	48	Para-1	Irregular bleeding	Type 1	Curettings (AH 2+Ca)	9 years
73	48		P.M.B.	Type 1	Uterus (Ca)	3 months
89	51		P.M.B.	Type 1	Curettings (Ca)	3 years
19	27	Nullipara	7 years amenorrhoea, then bleeding. Obesity	Type 2	Curettings (Ca)	7 years
41	52	Para-4	Severe menorrhagia	Type 2	Uterus (Ca)	1 week
68	45		Continuous bleeding for 12 months	Type 2	Curettings (Ca)	3 years
1	42	Para-1	Pain and menorrhagia for 12 months	Type 3	Uterus (Ca)	9 years
10	37	Nullipara	Amenorrhoea for 2 years	Type 3	Uterus (Ca)	4 months
28	50	Nullipara	Irregular periods for 12 months	Type 3	Uterus (Ca)	3 months
84	63		P.M.B.	Type 3	Uterus (Ca)	2 months
110	75		Recent bleeding	Type 3	Uterus (adeno-acanthoma)	2 months

remaining 10 all had subsequent curettage. The findings in the curettings can be summarized thus:

Type 1 on Initial Curettage

One case: same one year later.

Type 2 on Initial Curettage

Two cases: no evidence of atypical hyperplasia 3 months and 15 months later.

Three cases: same 10 months, 1 year and 5 years later.

One case: Type 3 atypical hyperplasia 2 years later.

Type 3 on Initial Curettage

Three cases: all showed no evidence of atypical hyperplasia 2 months, 8 months and 10 months later.

(4) In 24 of the remainder of the 128 cases atypical hyperplasia and carcinoma were diagnosed from the same material. In 19 cases the diagnosis was made from curettings and in 5 from examination of the uterus. In 10 the hyperplasia was classed as Type 2 and in 14 as Type 3.

(5) In the remaining 11 cases the diagnosis of atypical hyperplasia alone was made from examination of the uterus without previous curettage being performed.

DISCUSSION

In this series of 128 cases of atypical hyperplasia there are 24 in which carcinoma and atypical hyperplasia were present concurrently. In another 12 carcinoma was found after an initial diagnosis of atypical hyperplasia months or years previously. In a further 60 patients hysterectomy was performed after an initial diagnosis of atypical hyperplasia and another 11 cases were first diagnosed after hysterectomy. Of the remaining 21 cases 11 had subsequent curettage but not hysterectomy and 10 were not followed.

The progress of the 60 cases mentioned above is as follows. Twenty cases had no evidence of the lesion after adequate examination of the uterus. Forty cases still showed atypical hyperplasia. In 15 it was less marked than in the original material, in 14 it was the same and in 11 it was more marked. Of the latter, 7 had their hysterectomy within three months, 2 between three and six months and 2 more than a year after the original diagnosis.

Of the 12 cases in which carcinoma of the endometrium was found after a primary diagnosis of atypical hyperplasia, 4 were classed as Type 1, 3 as Type 2 and 5 as Type 3. The average interval between the diagnosis of atypical hyperplasia and of carcinoma for Types 1 and 2 combined was 4·4 years, although 2 cases had hysterectomy within three months.

Of the Type 3 cases, 4 had hysterectomy within three months and 1 after 9 years. Excluding the cases of probably co-existent atypical hyperplasia and carcinoma there are 6 cases in which the hyperplasia would appear to have been a pre-cancerous lesion and 5 of these were of a histological type which would not be mistaken for carcinoma.

It is important to be aware of the fact that carcinoma may be present in the uterus when only atypical hyperplasia is seen in the scrapings. In the 12 cases just referred to there were 6 in which this may have happened. Further evidence for the association of atypical hyperplasia and carcinoma is the group of 24 cases with separate lesions diagnosed at the same time. In 10 of these the hyperplasia was classed as Type 2 and in 14 as Type 3.

It is well known that many patients remain free of atypical hyperplasia after curettage of the uterus. Observation of the sites of the atypical endometrium in hysterectomy specimens offers a possible explanation for the variable outcome in these patients. In some cases the lesion is confined to a polyp and permits of complete removal while in others it reaches to the basal layers of the mucosa, or dips irregularly into the underlying muscular wall.

Treatment

In Type 3 cases of atypical hyperplasia hysterectomy appears to be the logical mode of treatment. For Type 2 cases hysterectomy is also advisable unless the patient can be kept under close observation and curetted again if symptoms persist. However, even in such cases, carcinoma has occasionally been observed years after the original diagnosis. Young age may be one of the factors in deciding whether observation or hysterectomy would be the wisest course.

Too conservative an attitude, however, may be unwise in this regard, particularly if the lesion belongs in the Type 3 class or the patient is unduly obese.

Conclusion

This study confirms that patients with atypical hyperplasia are more likely to have an associated carcinoma of the uterus or develop it subsequently than are those with the common benign hyperplasia of the endometrium. Furthermore, the likelihood increases as the atypical features of the condition become more marked. In some cases no hard and fast line can be drawn, in the examination of scrapings, between atypical hyperplasia and carcinoma. Treatment for the more severe forms of atypical hyperplasia is, as set out above, usually simple hysterectomy. More radical procedures are not indicated.

Summary

(1) A study of 128 cases of atypical hyperplasia is presented.

(2) The criteria for the diagnosis of the condition are set out.

(3) The average age at which the condition is found is 50 years and the main symptoms are irregular or continuous bleeding or excessive menstrual loss.

(4) It is suggested that an arbitrary grading into three types is helpful in assessing the prognosis in the individual case. On this basis, the association or later development of carcinoma in the three types rises from 15 per cent in Type 1 to 45 per cent in Type 3.

(5) The treatment is briefly discussed.

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TWIN PREGNANCY IN A SEPTATE UTERUS

BY

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TWIN pregnancy in the septate uterus is seldom reported in the literature, septate uterus being one of the less common congenital uterine abnormalities. In reviewing series of cases of congenital malformations of the reproductive tract in association with pregnancy, Fenton and Singh (1952) found 5 cases of septate uterus in a total of 96 cases; Baker *et al.* (1953) 6 cases in a total of 127; Philpott and Ross (1954) 2 cases in a total of 41; and Blair (1960) 1 case in a series of 68 cases.

Septate uterus may be regarded as a type of double uterus, accepting the simple definition of the latter given by Hunter (1957). Reports of twin pregnancies in other types of double uterus are more common. In recent years, Williams and Cummings (1953) have reported a case in a complete double uterus, Brown (1956) a case in a uterus pseudo-didelphys, and Vartan (1958) a case in a uterus didelphys.

Twin pregnancy in the septate uterus was first reported by Kickham (1922), who, at that time, could find no other record in the literature. In his case, the condition was found when a Caesarean section was performed, at term, on a patient suffering from pre-eclampsia. Twins, weighing 6 pounds and 6 pounds 14 ounces, were delivered. The mother unfortunately died following convulsions in the puerperium.

Another case was reported by Rauch (1938) when twins weighing 4 pounds and 4 pounds 8 ounces were delivered *per vaginam*, one month prematurely. One placenta was delivered spontaneously but the other remained adherent to the septal angle. Repeated attempts at manual removal failed and a hysterectomy was performed.

In the series of cases reported by Fenton and Singh (1952), there is one case of twin pregnancy in a septate uterus, but no details are given.

In view of the rarity of the condition, the details of the present case seem worthy of record.

CASE REPORT

Mrs. M.R., aged 25 years, was first seen at the antenatal clinic on 28th September, 1959.

Past Medical History. An appendicectomy had been performed in 1942.

Past Obstetric History. Para-1; gravida-2. The first confinement in March, 1959, took place in another hospital. Labour commenced prematurely at the 35th week. In the 2nd stage of labour, a vaginal septum, previously detected, was excised and delivery completed by forceps extraction. The baby, a live female, weighed 5 pounds 14 ounces. The placenta was delivered spontaneously but there was a blood loss of 20 ounces. The patient was noted to have a double uterus.

Present Pregnancy. The last normal menstrual period had commenced on 5th June, 1959, the expected date of confinement being 12th March, 1960.

At the first antenatal visit, the uterus was symmetrical in shape, but was noted to be large for the period of gestation. On speculum examination there was a single cervix, with a patulous os and a mid-line septum.

On 7th December, 1959, the uterine fundus had reached a level 4 finger-breadths above the umbilicus. Foetal parts could not be palpated and no foetal heart sounds were heard. A radiograph was taken and showed twins of 24-weeks gestation, lying parallel, one presenting by the head and the other by the breech.

From the 28th week of pregnancy, the uterine fundus exhibited a marked dip at the mid-point.

At the 32nd week of pregnancy the patient developed ankle oedema which persisted in spite of rest, although there was no hypertension, no proteinuria and no anaemia. Both foetuses now presented by the head.

At the 35th week of pregnancy there was some increase in oedema and the diastolic blood pressure rose to 90 mm. Hg. The patient was admitted to hospital for rest and

was treated with sedatives and diuretics, but the oedema persisted and the blood pressure was unstable.

At the 37th week there was a rise of blood pressure to 160/100 mm. Hg, the oedema increased and a trace of protein appeared in a catheter specimen of urine. The uterus now felt very tense and the fundus was at the level of the xiphisternum. The foetuses were lying parallel, both presenting by the head and both heads lying at the same level above the pelvic brim. On examination *per vaginam* the cervix was found to be patulous and oedematous, and it was confirmed that neither head was entering the pelvis.

An elective Caesarean section was performed under general anaesthesia on 19th February, 1960. The abdomen was opened through a midline sub-umbilical incision. The uterus was palpated to determine the nature of the deformity. Externally the uterus appeared as a single organ with one uterine tube at either side. There was a palpable dip in the fundus and from this a puckered line stretched down the middle of the anterior uterine wall (Fig. 1). A transverse incision was made in the lower uterine segment to the left of the mid-line and a live female child, weighing 5 pounds 10 ounces, length 18 inches (45 cm.) and head circumference 31·2 cm., was delivered. The head was markedly narrowed from side to side as if subjected to lateral compression.

The septum could now be seen bulging into the left half of the uterus. A second transverse incision was made to the right of the mid-line, avoiding the septum, and a live male child, weighing 6 pounds 7 ounces, length 18 inches (45 cm.) and head circumference 34·8 cm., was delivered.

The uterus was brought out through the incision for the purposes of photography. Ergometrine maleate 0·5 mg. was injected intravenously and both placentae were expelled spontaneously with minimal blood loss whilst the photographs were being taken (Fig. 2). Exploration of the uterus revealed a mid-line septum, approximately 2·5 cm. thick near the fundus. The septum stretched from the fundus down through the uterus and cervical canal, gradually thinning out to a $\frac{1}{2}$ cm. thickness in the cervical portion. The septum is shown in Figure 3. The uterine incision was repaired and the wound closed.

Both babies cried immediately at birth and made good progress. The puerperium was uncomplicated, but breast feeding was not successful. The mother and her infants were discharged on the 14th post-operative day.

When seen six weeks later the mother was in good health and there had been no abnormal bleeding. On examination the uterus was found to be anteverted, mobile and slightly bulky. There was a small cervical erosion. The patient is being kept under review.

Summary and Discussion

A report is presented of a twin pregnancy in a septate uterus. A double uterus had been diagnosed at the first confinement when a vaginal septum had been excised. In the absence of this knowledge the diagnosis might have been suspected from the presence of a marked dip in the uterine fundus and from the persistent parallel lie of the foetuses, with both heads lying, side by side, at the same level above the pelvic brim. The occurrence of a concomitant pre-eclampsia precipitated the decision to effect delivery by Caesarean section at the 37th week.

The main hazards associated with pregnancy and labour in the double uterus are premature labour, ante-partum haemorrhage, malpresentations, uterine dysfunction, placental insufficiency and faulty separation of the placenta leading to third stage complications and post-partum haemorrhage. These risks are stressed in papers by Falls (1928), Puddicombe (1929), Jarcho (1946), Fenton and Singh (1952), Philpott and Ross (1954) and Hunter (1957).

In view of the many possible hazards, the presence of twins, and the associated pre-eclampsia operative delivery in this case seemed fully justified. In addition, both foetal heads lay at the same level above the pelvic brim, with neither attempting to enter the pelvis, thus making induction of labour inadvisable.

Acknowledgments

I wish to thank Dr. Susanne J. Paterson for her encouragement and permission to publish this case. My thanks are due also to Mr. J. H. B. Shearsby and his staff, from the Department of Obstetrics and Gynaecology, Edinburgh University, who so kindly arranged the photography at operation.

FIG. 1

External appearance of septate uterus showing arrangement of musculature.

FIG. 2

Placentae delivering simultaneously from each half of a septate uterus. The white arrow points to the septum.

FIG. 3

Septate uterus after delivery of twins by Caesarean section.
The thick mid-line septum is clearly demonstrated.

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DYSGERMINOMA OF THE OVARY IN PREGNANCY

Case Report and Commentary

BY

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DYSGERMINOMA of the ovary during pregnancy is exceedingly rare, only 14 cases having been recorded. In a review of 427 cases of dysgerminoma in the world literature, Mueller, Topkins and Lapp (1950) reported 11 cases associated with pregnancy. Since then 1 case was reported by Watson (1956) and a second by Misra (1958).

CASE REPORT

Mrs. B.L., aged 30 years, was expecting her 3rd baby in the 3rd week of August 1958 (date uncertain). Her first 2 pregnancies and labours had been uneventful; the 1st child was 9 years and the 2nd 3 years of age.

Her previous menstrual history was katamenia at 15 years with periods every 28 days lasting 7 days. She was seen at the hospital antenatal clinic for the 1st time at 16–18 weeks pregnancy. The uterus corresponded to the approximate period of amenorrhoea and no other abdominal or pelvic tumour was noted. Her subsequent antenatal examinations were at the Borough Antenatal Clinic until the 34th week after which she attended the hospital. At 34 weeks the presentation was a breech; spontaneous version occurred but 4 weeks later it was a breech again, and external cephalic version was performed and the child remained as a vertex presentation, left occipito-anterior to term.

At 38-weeks pregnancy an unusual swelling was noted towards the right flank and high up near the uterine fundus. It felt about 4 inches (10 cm.) in diameter and it was the same consistence as the uterus away from foetal parts. No uterine contractions occurred during palpation and it was impossible to tell whether the swelling was due to sacculation of the uterus, or whether it was an ovarian tumour lifted very high in the abdomen, or possibly a very soft uterine fibroid. The patient had no discomfort from it and no tenderness. She went into spontaneous labour and had a normal delivery of a healthy boy weighing 8 pounds 9 ounces (3,883 g.) on 25th August with no complications in labour.

During the puerperium it became obvious that the right-sided swelling was a firm cyst, slightly oval in contour about 7 inches long and 5 inches wide (17·8 cm. × 12·7 cm.) distinct from the uterine fundus which involuted normally. It was still symptomless and was presumed to be an ovarian cyst.

Operation was performed on the 7th day of the puerperium. A little clear fluid was found in the peritoneal cavity. The right ovary was entirely replaced by a soft solid tumour which was yellow and reddish purple in colour and was very vascular on its surface. The left ovary and the uterus and both tubes appeared normal.

Right oöphorectomy was performed. The left ovary was not removed because it was hoped that the tumour might be non-malignant and that its haemorrhagic appearance was only due to trauma from the recent labour.

The tumour measured $7\frac{1}{2} \times 5 \times 4$ inches (19·5

cm. × 12·7 cm. × 10·9 cm.) and the pedicle was 1½ inches (4·3 cm.) thick. It weighed just under 3 pounds (1,338 g.). On section it was found to be soft solid and cystic in places with purplish and yellow coloration right through. Histological examination showed it to be a dysgerminoma with typical seminoma-like cords with lipoid stroma and lymphocytes. Many cells were hyperchromatic and there were numerous mitotic figures. The appearances suggested a very actively growing malignant neoplasm.

In view of this report and the fact that the patient now had 3 children it was advised that she have a total hysterectomy and removal of her tubes and the left ovary. This was performed 14 days later. There was no evidence of tumour in these structures on macroscopic or microscopic examination and no evidence of spread in the peritoneal cavity or liver.

The patient made a good post-operative recovery and remains well without any evidence of recurrence of tumour 2½ years later.

Commentary and Review of Literature

Incidence of Dysgerminoma

The incidence of dysgerminoma in 427 patients was found to be 1·1 per cent of all ovarian tumours and 4·7 per cent of malignant ones by Mueller, Topkins and Lapp (1950) and the age incidence varied from 2 to 76 years. An incidence of 3 per cent among malignant ovarian tumours was found by Abel (1957) and Pedowitz, Felmus and Grayzel (1955) were able to find only 540 cases of dysgerminoma in the world literature.

Dougherty and Lund (1950), in a review of the literature over the previous 15 years, found 9 cases of dysgerminoma among 36 solid ovarian tumours complicating pregnancy. Hughesdon (1959) states that dysgerminoma is the rarest ovarian tumour in this country and the only cases previously reported complicating pregnancy in this country have been those of Stabler and Thomson (1937) and Abernethy (1943).

In the 14 cases so far recorded the age incidence varied from 18–35 years and in 10 patients it was the first pregnancy, 2 the second, 1 the third and 1 the sixth. The patient here recorded was in her 3rd pregnancy.

Complications

The most frequent complication reported has been obstructed labour necessitating Caesarean section. This occurred in 5 cases, those of Stabler and Thomson (1937), Nyst (1940), Cunningham and McGrath (1942), Abernethy (1943) and Watson (1956). In a 6th case reported by Schneider and Vesell (1947) the tumour was impacted in the pelvis in her second pregnancy, but not in her first. It was removed when Caesarean secton was performed at the 38th week, before the onset of labour, and it was noted to be approximately the same size as when it had been discovered during a forceps delivery 2 years previously. She did not return to hospital for its removal then so presumably it had caused no symptoms during or after the 1st pregnancy.

Another case with no complications was reported by Szathmary (1933). Her tumour was discovered during a manual removal of the placenta after a normal delivery at term. It was removed 6 weeks later and was combined with tuberculosis of the adnexa.

Abdominal pain in the 1st week after normal delivery occurred in the case reported by Doubrère (1933). The patient was delivered by a midwife and when seen on the 8th day of the puerperium because of the pain a tender tumour was found in the abdomen and it was removed.

Intestinal obstruction occurred during the puerperium in the case of Le Gac (1935). This tumour was not discovered until the 2nd week of the puerperium when a loop of ileum became obstructed by adhesions to a large ovarian tumour lying high in the abdomen which was removed with difficulty because of the bowel distension and adhesions.

Clinical malignancy in the dysgerminoma at the time of operation was found only in 1 case, that described by Cunningham and McGrath (1942). Both ovaries were extensively involved and secondary deposits were present at the time of Caesarean section at 39-weeks pregnancy. This patient had been well until the 36th week when vomiting occurred but in the 3-weeks interval became ill. She died 14 months later having had only temporary improvement following removal of the ovaries and radiotherapy. The child was healthy. Clinical malignancy

developing later is only recorded by Doubrère (1933). This patient developed a tumour in the other ovary and pelvic secondaries 1 year after removal of the 1st ovary. The 2nd ovary and the uterus were then removed and radiotherapy given and the patient remained well 2 years later.

In 5 cases the tumours were removed in early pregnancy apparently without having caused any symptoms; in 3 of these, those reported by Dockerty and MacCarty (1939), Lorber and Vesell (1940) and Schomaker, Glascock and Chapman (1947) the tumours were removed in the 2nd or 3rd months of pregnancy and the pregnancies went to term, healthy infants being delivered. In 1 case, also recorded by Szathmary (1933), the tumour was removed at 5-months pregnancy and a very macerated foetus weighing 4,000 g. was delivered near term, and in the 5th, recorded by Misra (1958), the tumour was removed at 25-weeks maturity and the patient miscarried shortly afterwards but had a successful pregnancy in the following year.

Treatment and Prognosis

Among the 14 recorded cases removal of the ovary containing the dysgerminoma was the only treatment in 12 patients and of these 9 are reported as well at follow-up examination 1 to 7 years later, 8 being 2 years or longer. No follow-up is mentioned in the other 3 cases. One case, that of Cunningham and McGrath (1942), had bilateral oöphorectomy followed by radiotherapy because of clinical malignancy at the time of Caesarean section, and a 2nd reported by Doubrère (1933) had removal of 1 ovary a week after delivery, and the 2nd ovary and uterus a year later and subsequent radiotherapy because of recurrence. Only the 1st of these patients died, the 2nd being well 2 years later. The case now recorded had removal of 1 ovary a week after delivery and the 2nd ovary and the uterus 2 weeks later and she remains well after $2\frac{1}{2}$ years.

In the review by Mueller, Topkins and Lapp (1950) of 427 cases the degree of malignancy is stated to vary considerably, but the mortality is given at 27·3 per cent. Pedowitz, Felmus and Grayzel (1955) give a mortality of 72·9 per cent in a review of 102 cases reported since 1949 with a 5-year follow up in 70. They found that the prognosis was worse in girls under 15 years of age and women over 40 years, but even between these ages the mortality was 60 per cent. though very few developed recurrences if they remained well for 2 years. It is apparent that the majority of patients having dysgerminoma associated with pregnancy are in the more favourable age group. Pedowitz *et al.* (1955) consider that the tumour is sufficiently malignant to remove both ovaries and the uterus even in young women and recommend that the abdomen should be reopened for this when the diagnosis is established. Their assertion is strengthened by the fact that 2 cases who had unilateral oöphorectomy when not pregnant required irradiation in the puerperium for recurrences after subsequent pregnancies. Against this view, however, is the fact that the cases reported by Stabler and Thomson (1937), Lorber and Vesell (1940) and Misra (1958) all had subsequent pregnancies without recurrence of tumour.

Should secondary deposits develop radiotherapy is recommended as the tumour is usually radio-sensitive, but from consideration of the cases so far recorded it does not appear that the prognosis for patients suffering from dysgerminoma is really made worse by pregnancy.

Summary

A case is recorded of dysgerminoma of the ovary in pregnancy in a gravida-3 with no complications in the pregnancy, labour or early puerperium. The tumour was removed a week after delivery and, as the appearances suggested an actively growing neoplasm, the other ovary and uterus were removed subsequently.

The literature is reviewed and prognosis and treatment considered.

Acknowledgments

My thanks are due to Dr. R. A. B. Drury and Dr. P. E. Hughesdon for their advice on the histology of the tumour.

Addendum

Since this paper was written a further case of dysgerminoma of the ovary discovered in preg-

nancy has been reported by Liebert and Stent (1960) and this tumour was further complicated by chorionepithelioma in it. The patient died 7 months after removal of the tumour in late pregnancy, from recurrent chorionepithelioma.

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POTASSIUM PERMANGANATE AS A CAUSE OF ANTE-PARTUM HAEMORRHAGE

BY

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INTRODUCTION

POTASSIUM permanganate burns of the vagina in early or suspected pregnancy have been widely reported. It is much less common for bleeding from the birth canal in the last trimester to have the same cause. In the case recorded here the painful contractions of labour were simulated, and appeared to support a diagnosis of uterine haemorrhage.

CASE REPORT

Mrs. M.W., was admitted to hospital in April, 1959, bleeding heavily *per vaginam*. It was estimated that a soaked bath towel contained at least 2 pints (1·1 litres) of bright red blood. The patient said that bleeding had begun painlessly an hour earlier, on her return home from work, and that bearing-down pains had been coming regularly in the last half hour.

By her dates she was in the 36th week of pregnancy. Three previous children by a different consort had all been delivered normally around term. The youngest was 4 years old and the heaviest was 10 pounds 8 ounces (4·8 kg.) at birth.

On examination the patient was pale and drowsy with a warm dry skin, her pulse was of good volume at 84/minute and blood pressure 140/90 mm. Hg. The uterus was of a size consistent with the dates, the breech presented and was not engaged in the pelvis. The foetal heart rate was 172/minute with minor variations in rhythm. Weak uterine contractions were felt through the abdominal wall. Slight oedema of fingers and legs was present. A catheter specimen of urine was albumin free.

With a provisional diagnosis of partial separation of a placenta praevia, arrangements were made for examination under anaesthesia followed by Caesarean section if necessary. Cross-matching of blood of the appropriate group was begun and a slow drip infusion of intravenous normal saline commenced. The haemoglobin was 12·4 g. per cent.

At the examination the cervix was closed. An elongated black-based ulceration of the posterior vaginal wall extended downwards 2 inches (5·1 cm.) from the fornix. It was bleeding freely. The vagina was irrigated with normal saline and the ulcer obliterated by 3 transversely running sutures of chromic catgut. A flavine gauze pack in the vagina was removed 24 hours later.

On direct questioning next day the patient said she had inserted 2 potassium permanganate tablets into the vagina a half hour before bleeding had begun. In the 48 hours following operation the fluid balance charts showed a urinary output of 72 ounces (2·04 litres). The serum bilirubin was 0·6 mg./100 ml., and at the end of that time the haemoglobin level had fallen to 10·3 g./100 ml.

Healing was assessed 14 days after admission. A narrowing of the upper vagina was present but of more importance was the fact that the rectal mucosa was completely adherent to the region of the ulceration. It was decided that vaginal delivery, even were it possible, would expose this scar tissue to the risk of rupture and recto-vaginal fistula formation.

Elective Caesarean section at term was planned. The patient went home with 3-weeks supply of ferrous gluconate tablets. On the 29th day after the haemorrhage she was admitted in

early labour and a 4 pounds 9 ounces (2·07 kg.) living male infant delivered by lower segment Caesarean section.

Discussion

Potassium permanganate may be introduced into the vagina as tablets, crystals, or in solution. The 2 gr. and 5 gr. tablets are most commonly used in an attempt to procure abortion. Accidental administration of undissolved tablets or crystals can occur in douching.

The immediate danger of haemorrhage was reported by Shull (1941) in America and Miller (1951) in England. It is borne out by nearly all other reports (McDonough, 1945; Alment and Nicol, 1953). Kobak and Wishnick (1955) recorded the sequel of intestinal obstruction. In their case and others Caesarean section has been necessary later. Death due to douching with this agent causing methaemoglobinaemia was reported by Jetter and Hunter (1949).

In the case recorded here the bearing-down pains were attributed to rectal irritation from the adjacent burn. It is believed that the strong caustic action of permanganate is due to the release of nascent oxygen and the formation of potassium hydroxide.

The value of examination under anaesthesia is demonstrated. Had this been omitted Caesarean section may well have delivered a foetus too premature to survive and the source of haemorrhage would have remained. It is surprising that fistula-formation is not a more common sequel in such cases.

Acknowledgment

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DISSECTING ANEURYSM ASSOCIATED WITH PREGNANCY

Report of a Case

BY

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ABOUT 1 per cent of all sudden deaths are due to dissecting aneurysm (Mote and Carr, 1942). Hospital records (Wood, 1956), which include relatively few such deaths, give an approximate incidence of one dissecting aneurysm in every 450 necropsies. Dissecting aneurysm of the aorta usually occurs in older individuals, particularly in the presence of hypertension. Men are more susceptible than women with a ratio of 2·5 to 1 (Levinson *et al.*, 1950). However, dissecting aneurysm of the aorta is by no means uncommon in young individuals. It has been pointed out by Schnikter and Bayer (1944) that, when the disease occurs in young females, it is frequently in association with pregnancy.

CASE REPORT

Mrs. M.S., aged 32, was first seen at the antenatal clinic on 8th June, 1959, when she was in the 14th week with her second pregnancy, the first pregnancy, which was normal, being in 1952. She had a bilateral inguinal herniorrhaphy in 1946 and an appendicectomy in 1948.

At the time of booking her general condition was satisfactory. Her blood pressure was 120/60 and urinalysis was normal. The haemoglobin estimation was 81 per cent, and her blood group was AB Rhesus positive. The Wassermann and Kahn tests were negative, and a routine chest X-ray showed no abnormalities (Fig. 1).

Pregnancy progressed normally. Her blood pressure remained normal throughout and the urine was always free of albumin. The haemoglobin at the 36th week was 77 per cent. She had a spontaneous onset of labour on 22nd October, 1959, followed by normal delivery of a living male infant weighing 8 pounds 10 ounces. The labour lasted 8 hours 10 minutes in all, the blood loss being only 10 ounces. The blood pressure after the delivery was indicated to be 120/80.

For the next 3 days the baby and mother were well. The patient's body temperature was normal, pulse 70–80, respiration 20. On the 4th puerperal day, soon after feeding the baby, she was seized suddenly with severe chest pain. The pain was felt mostly between the scapulae referred slightly to the left and anteriorly behind the sternum. The pain was worse on respiration, and the attack lasted a few hours. She had no cough or sputum. The body temperature was 97·6° F., pulse 90 and respiration 88 per minute. The blood pressure was 180/80.

Examination of the chest showed that the trachea was central and no tracheal tug was present. The lung fields were clear. There was no cardiac enlargement clinically, but a soft systolic murmur was heard at the apex. Examination of the abdomen showed no abnormal findings and there was no evidence of deep vein thrombosis in the lower limbs. A provisional diagnosis of pulmonary embolus was made and morphia gr. ¼ was given.

The patient had two further attacks in the following 3 days. She was never shocked during an attack, though the pain was described as severe and lasting about 1–2 hours. She remained afebrile. The pulse and respiration were normal, whilst the blood pressure remained high. Repeated examinations of the chest showed that the lung fields were clear. However, the systolic

FIG. 2
X-ray taken in the puerperium showing a bulge to the left of the descending aorta.

FIG. 1
X-ray taken at 14th week of pregnancy.

murmur heard previously at the apex was found to propagate into the epigastrium, and to be conducted as far down as the left iliac fossa. It was also audible posteriorly at the region of the lower thoracic and lumbar spine as far down as the sacrum. It was also noted that the right femoral pulse was barely palpable, while distal pulsations on the same side were absent. However, there was no evidence of ischaemia in either of the lower limbs. No neurological signs were present.

Laboratory investigations showed a haemoglobin of 108 grams (73 per cent), leucocytes 13,000 per c.mm., with 81 per cent polymorphs, 15 per cent lymphocytes, 1 per cent monocytes and 3 per cent eosinophils. The erythrocyte sedimentation rate was 53 mm. in the first hour. The blood urea was 33 mg./100 ml. A clear specimen of urine showed a trace of albumin and some epithelial cells only.

An E.C.G. showed no abnormalities, whilst a chest X-ray, when compared to the one taken at booking, showed a bulge to the left of the descending aorta (Fig. 2). The arch of the aorta had a normal outline. The lung fields were clear.

A diagnosis of dissecting aneurysm was finally made for which no immediate treatment was necessary.

In November, 1959, the patient was getting some claudication in the buttock and thigh on walking, but had no further episodes of pain in the chest. As it was considered to be an inadvisable risk for the patient to embark upon another pregnancy, she was sterilized on 13th January, 1960. At laparotomy the aneurysm was felt well involving the abdominal aorta down to, but not involving, the bifurcation. The aorta was tortuous and displaced to the left. Weak pulsations were felt in both iliacs.

The patient is alive and is able to carry on with ordinary household duties. She had no further attacks of chest pain and she did not suffer from any more claudication. She is still being followed up as a medical out-patient.

Discussion

Schnikter and Bayer (1944) collected 141 cases of dissecting aneurysm under the age of 40 from the literature up to 1944. They emphasized the fact that, out of a total of approximately 580 cases of dissecting aneurysm of all age groups on record, 141 or 24·31 per cent, approximately one in four, were under 40 years of age. The most interesting feature that presented itself in their series of cases was the association of dissecting aneurysm of the aorta with pregnancy. Out of a total of 49 females in their series, in 24 or 49 per cent, the accident occurred in association with pregnancy. Uebermuth (1933) thought this to be related to the strain and blood pressure changes that are known to occur during labour. However, Schnikter and Bayer, after analyzing the series, found that this could not be the causative factor for the majority occurred during the last trimester before labour had begun. In only two cases was the dissection said to have occurred "with labour pain". In 2 cases the accident occurred post-partum, one 12 days and another 3 weeks after delivery. Most cases were primigravidae. The largest number have occurred at the eighth to ninth month, and this is of interest in view of the altered circulatory dynamics at this stage of pregnancy.

Aetiology

Schnikter and Bayer (1944) concluded that hypertension is not of paramount importance in the causation of dissecting aneurysm, at least in the younger age group. Only half of the cases in their entire series (all age groups), in which the blood pressure was recorded, had hypertension, and that only 2 of the 24 cases with pregnancy had hypertension.

What is of importance is an abnormal media, which was described by Erdheim (1920) as cystic medial necrosis. The cause of such necrosis was thought to be due to obliterative endoarteritis though this is not confirmed. It has recently been suggested that cystic medial necrosis and dissecting aneurysm may be due to defective formation or excessive destruction of chondroitin sulphate, the chief mucopolysaccharide of the ground substance of the aorta (Ponseti and Baird, 1952).

Finally, as pointed out by Schnikter and Bayer (1944), the altered lipid metabolism which is known to occur during pregnancy may play some role in the occurrence of dissecting

aneurysm during gestation. Leary and Weiss (1940) report an instance of a rabbit fed on cholesterol for approximately 156 days in which a dissecting aneurysm, very similar to that seen in man, occurred spontaneously. In further experiments with animals these authors were unable to induce a dissecting aneurysm by high cholesterol feeding alone, although medial changes occurred, but they could produce it by subsequent injection of adrenaline causing hypertension.

Clinical Features

Dissection of the aorta may be precipitated by effort (Gager, 1928) but is more often spontaneous.

The commonest symptom is severe pain in the chest, which usually lasts for some hours. The pain usually is retrosternal and in the back, between both scapulae. It may be referred to the head and neck, and less often to the arms (Baer and Goldburgh, 1948).

Breathlessness is also common. Syncope occurs in about 10 per cent of cases. Attacks may therefore resemble coronary thrombosis, but in cases that survive the blood pressure usually remains high and the electrocardiogram normal. Moreover, in dissecting aneurysm, dilatation of the aorta may often be seen in skiagrams.

The heart is usually enlarged and a systolic murmur at the apex and over the aortic arch is generally present. Quite frequently there is the development of a diastolic murmur suggestive of aortic regurgitation. This is caused by dilatation and deformity of the aortic ring resulting from dissection.

A systolic murmur and thrill may develop over partly occluded vessels involving the aorta (McGeachy and Paullin, 1937). The widespread radiation of this murmur as evidenced in this case seems to have some diagnostic significance especially in cases of dissecting aneurysm involving the abdominal aorta.

Fever and leucocytosis are usually present. There is an increase in the polymorphonuclear leucocytes. If bleeding (into the aorta, pericardium or pleura) is extensive enough, severe progressive anaemia may develop in a few hours. The urine may show a trace of albumin. If dissection has approached or involved the renal arteries, haematuria or even uraemia may predominate in the symptom complex.

The duration of life after the attack is perhaps a little longer in the younger age group, possibly because of their otherwise better physical condition (Schnikter and Bayer, 1944). According to Shennan (1934) about 10 per cent of all dissecting aneurysm recover from the attack, usually owing to rupture re-entry.

Summary

(1) A case of dissecting aneurysm of the aorta occurring in a female of 32 years, 4 days post-partum, is presented.

(2) A review of the literature of cases of dissecting aneurysm in the younger age group and associated with pregnancy is given.

(3) Some aspects of the clinical picture are discussed.

My thanks are due to Mrs. J. Bryson and Mr. S. Savage for permission to write up the case.

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BED REST IN TWIN PREGNANCY

BY

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NEARLY ten years ago it was first advocated that women in twin pregnancy should be rested in bed for part of the third trimester in an attempt to reduce the immaturity rate amongst the babies (Bender, 1952; Russell, 1952). Anderson (1956) several years later was a little more cautious, saying that antenatal rest in hospital appeared to help prolong the pregnancy, but the effect might be very slight. Guttmacher and Kohl (1958) were just as guarded ". . . the likelihood of postponing the onset of labour until the end of the thirty-fifth week is probably increased by hospitalization and bed rest beginning at the thirtieth to thirty-second week . . .". Donald (1959), still continuing in this cautious vein, shifted the emphasis slightly by suggesting that girth was more important than length of gestation when deciding the time for bed rest.

With all these guarded statements about the value of bed rest in twin pregnancy in the literature, but its fairly wide acceptance in practice, it was considered fit to analyze the results so far in this hospital, where it has been the increasing policy to admit twin pregnancies for a period of rest between the 30th and 36th weeks.

MATERIAL AND METHODS

The period under review was 1953 to 1958. Apart from the slightly high incidence of multiple pregnancies the cases were unselected, coming from all of the Registrar General's social classes. A review of the notes failed to detect any change in the management of twin pregnancy during the six years other than the factor under examination.

There were 158 multiple pregnancies in the years 1953 to 1958. These were placed in three groups using a similar scheme to an earlier study (Anderson, 1956):

Group A: (64 pregnancies) consisting of all the patients who had no bed rest between the 30th and 36th weeks.

Group B: (60 pregnancies) consisting of all the patients who had at least 7 continuous days of bed rest in the period of the 30th to 36th week.

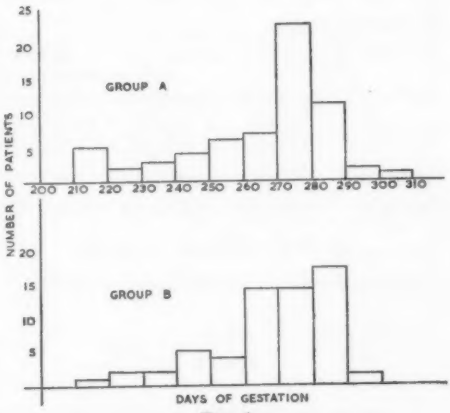

FIG. 1
Distribution of length of gestation.

Group C: (14 pregnancies) are patients who could not be included because of such things as premature rupture of the membranes, triple pregnancy, or termination of pregnancy before the 30th week.

If rest in bed does contribute to the lowering of foetal mortality, then it is reasonable to expect a significant alteration in the length of gestation and the birth weight, as well as the foetal mortality. A comparison was therefore made between the length of gestation, babies' weight and foetal mortality in Groups A and B.

Results

(a) *Length of Gestation*

Distribution of length of gestation see Figure 1.

$$\frac{\text{Total days of gestation of Group A}}{64} = 263{\cdot}73$$

Mean = 264.

$$\frac{\text{Total days of gestation of Group B}}{60} = 266{\cdot}96$$

Mean = 267.

Difference between Groups A and B = 3 days. This is not significant.

(b) *Babies' Weight*

	1st Twin Mean Weight	2nd Twin Mean Weight	Mean Weight of Combined 1st and 2nd Twins
Group A	2506·95	2484·5	2495·766
Group B	2599·99	2562·45	2581·175

Mean B—Mean A = 85·4G

Standard error of the difference = 37·284.

$$\frac{\text{Difference}}{\text{S.E.}} = \frac{85{\cdot}4}{37{\cdot}284} = 2{\cdot}29$$

Therefore the difference is significant at 5 per cent level but not at 1 per cent.

(c) *Foetal Mortality*

	S.B.	N.N.D.	Total
Group A:			
1st twin	2	3	5
2nd twin	3	7	10
Total	5	10	15

Proportion $\frac{15}{128} = 0{\cdot}1172$

Group B:			
1st twin	2	–	2
2nd twin	4	4	8
Total	6	4	10

Proportion $\frac{10}{120} = 0{\cdot}0833$

Difference between groups = ·0339. This is not significant.

Discussion

These results are not statistically significant to a level at which firm conclusions can be drawn. However, some observations can be made. Even in this small series, one would have anticipated a greater difference between the two groups. It may be argued that this is due to bias caused by the inclusion of women in Group B who were only rested a minimum of 7 days. However, most of the cases in Group B were rested from 3 to 4 weeks. Further, the period of gestation within Group B appeared to be unrelated to the amount of bed rest when the cases were statistically analyzed.

Supposing these results were significant, would 3 days longer gestation and 3 ounces in weight justify the prolonged bed rest? At what level can we convince the obstetrician that his antenatal beds are being well used, and the patient that her enforced bed rest is necessary? As yet the only guidance in this seems to have come from Bender (1952) who reduced his "immaturity" from 52·2 per cent to 43·2 per cent, using a birth weight of 2,500 g. as the criterion of maturity. It is doubted if the difference would have been significant if 2,000 g. had been substituted. The value of 2,000 g. was the one suggested in a large series as being the critical level for survival (Guttmacher and

Kohl, 1958). It is interesting to note that in the present small series the level of 2,000 g. was well exceeded by both groups. Further, it is apparent to anyone engaged in obstetrics that the early diagnosis of twins is not easy, and not uncommonly unsuspected before the 30th week. Of course, everyone likes to see twin pregnancies diagnosed early, obstetrician and patient alike; but to advise admission for rest by the 30th week is often a counsel of perfection.

Both groups terminated pregnancy on the average two weeks before the 280th day from the onset of the last menses. The means of the other studies were 256·2, 257·8 and 261·6 days (Guttmacher, 1939; Potter and Crunden, 1941; Nesbitt, 1957, respectively). The mean birth weight of both groups of twins was near to the 2,386 g. and 2,398 g. found by other investigations (Potter and Crunden, 1941; Nesbitt, 1957). Remarkably close when one considers race, parity and localities are all different. The date from this series showed that the mortality for the second twin is higher than for the first, in keeping with the findings of other series (Bender, 1952; Donnelly, 1956; Guttmacher and Kohl, 1958).

Professor Norman Morris (1959), who was closely associated with care of patients at the beginning of the period at U.C.H., is now of the view that it also reduces toxaemia in twin pregnancy. The present series is too small to consider from this point of view, but no obvious difference has been noted.

Summary

A small series in an obstetric hospital of twin pregnancy failed to show that bed rest causes a statistically significant increase in the length of gestation and birth weight.

The published work is still very vague as to when and how much a patient should be rested, and it is suggested that a trial should be established to elucidate these points. The value of such a trial is great, because if it failed to show a significant reduction in factors affecting foetal mortality there would be a big saving in the antenatal beds as well as a minimizing of the disruption of the family.

The results of this study confirm those of other series.

I am grateful to Professor W. C. W. Nixon for permission to publish this paper, and also for his original stimulating remark from which this paper grew. I am grateful also to Mr. J. D. Martin for his helpful criticism; and to Mrs. D. Harris of the Statistical Department of University College, London, without whose help there would have been no statistical analysis.

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BOARI OPERATION

A Useful Procedure in the Treatment of Uretero-vaginal Fistula

Report of Three Cases*

BY

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INTRODUCTION

IN recent years the greater possibility and practicability of extensive pelvic surgery for carcinoma of the cervix has placed a new emphasis on methods of repairing permanent ureteral damage. Previously, the drawbacks of surgery were the high mortality rate, and in a proportion of cases the occurrence of urinary tract complications, especially uretero-vaginal and less frequently a vesico-vaginal fistula. Due to the advent of better anaesthesia, knowledge of fluid and electrolyte balance of the body and its proper regulation in the post-operative period, chemotherapeutic and antibiotic drugs and proper selection of cases for radical operation, mortality has fallen considerably, but fistulae still persist and their gravity can be realized by the well-known fact that until recently the ultimate treatment of the uretero-vaginal fistula was nephrectomy (Merenyi, 1948; Millin, 1948) in 75 per cent of cases.

When the operation for restoration of the continuity of the ureter into the bladder is considered necessary, several problems may face the surgeon, the commonest being whether or not the length of the ureter to be implanted is sufficiently long to reach the bladder without subsequent tension on the splice. From the surgical laboratory of Federoff in St. Petersburg, Melnikoff (1912) published a masterly article on this subject and dealt with the problem and all the attempts to solve it that had been instituted up to that time. From his reports one finds that surgeons experimented with various structures to replace the damaged ureter. These include metallic tubes, blood vessel grafts, tubes of mesentery, peritoneum, muscular wall and Fallopian tubes. Small bowel was also used unsuccessfully then. All these procedures proved futile when a large segment of the ureter was destroyed and had to be replaced.

Of the various methods of bridging the gap, one is to mobilize the pelvic portion of the ureter so that the curvature of the ureter is lengthened; it is possible to shorten its course by several centimetres in this way (Millin, 1948). Another ingenious method, not very commonly used so far in gynaecological ureteral fistula, is the bladder flap operation, the description of which is the theme of the following paragraphs.

HISTORICAL EVOLUTION OF THE OPERATION

In 1894, Boari, an Italian surgeon, was reported to have done a flap operation on a dog and that the animal was alive and well four years after.

In 1932–33, Spies *et al.* (1933) carried out interesting experiments on the ureters of dogs at the Yale University School of Medicine and they described a novel flap operation for re-implanting the ureter into the bladder in dogs. Apparently they were trying to avoid strictures of the ureter which they found frequently formed when surgery was performed upon the lower one-third of a dog's ureter.

* Part of a thesis for the Ph.D. degree of the University of London in 1958.

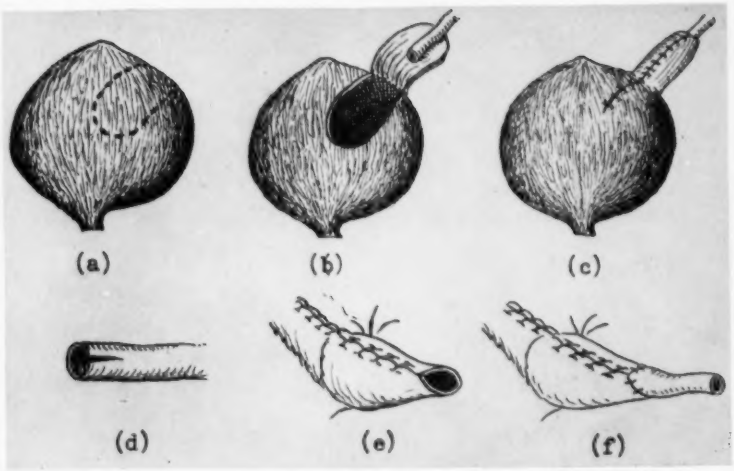

FIG. 1

Steps of the Boari operation. Figures d, e and f represent the method of fashioning the ureter according to Professor C. Scott Russell (*J. Obstet. Gynaec. Brit. Emp.*, 1956, **63**, 481).

FIG. 2

The right kidney is low in position. No other abnormality is seen in the renal tract (Table I, Case 1).

FIG. 4

Twelve weeks after Boari operation, showing no evidence of the right hydronephrosis and a normal urinary tract (Table I, Case 1).

FIG. 3

Seven and a half weeks after Wertheim's hysterectomy, showing right hydronephrosis. The left side appears normal (Table I, Case 1).

Ockerblad (1947) claimed that he was the first to make use of this ingenious flap method of performing a ureter implantation into the bladder in a human being. His patient, a woman of 44, developed a left uretero-vaginal fistula following total hysterectomy for multiple fibroids. Retrograde catheterization revealed that the left ureter was occluded 5 cm. from the vesico-ureteral orifice. Indigo-carmine injected intravenously did not appear from the left ureteral orifice, but did show in the vagina in 12 minutes. It appeared through the right ureteral orifice into the bladder in 4 minutes. Ockerblad opened the abdomen of the patient and found that the leak and obstruction were at 5 cm. level above the left ureteral orifice, and that the next few centimetres of the ureter had so degenerated that, in all, from 8 to 9 cm. of the lower end of the ureter was not worth using. Confronted with a ureteral stump too short to be re-implanted into the bladder, three methods of dealing with this case came to his mind, viz., nephrectomy, implantation into the bowel, or a Boari type of bladder flap operation hitherto never done on a human being. The operation was done on 30th September, 1936. Follow-up intravenous pyelogram a year later showed the splice like a narrow elongated diverticulum and no infection was present. Another pyelogram ten years later showed that the bladder flap had shrunk and looked like a slightly dilated ureter.

Materials for Study

In the present series, three patients were treated by this method for ureteral fistula following radical hysterectomy. The details of these cases are shown in Table I. These patients belonged to the Joint Carcinoma Clinic of the Chelsea Hospital for Women and the Royal Marsden (Cancer) Hospital, which was established in the year 1944. The function and results of treatment of this clinic have been described by Blaikley, Lederman and Simmons (1957).

Steps of the Operation

Briefly, the steps of the operation were as follows. Having opened the abdomen, the involved ureter was isolated with a Brunschwig flap of peritoneum below the pelvic brim. A square flap (Ockerblad used a flap 10 cm. in length and 4 cm. in width at its base) was taken from the superior surface of the bladder and folded backwards. It was converted into a continuous tube with two layers of catgut suturing (Fig. 1a to 1c). The ureter was

Table I

No.	Name and Age	Cause of Fistula	Pre-operative Pyelogram	Interval Between Opcration and Appearance of Fistula	Location of Fistula	I.V.P. Following Fistula	End Result of Boari Operation	Follow-up I.V.P. (12 Weeks Later)
1.	Mrs. M.A. .. (40 years)	Wertheim's hysterectomy for well-differentiated squamous cell carcinoma of the cervix (Stage II).	Normal (Fig. 2)	33 days	Lower end of right ureter.	Right sided hydronephrosis. Left side normal (Fig. 3).	Continence of urine achieved.	No evidence of right hydronephrosis (Fig. 4).
2.	Mrs. A.P. .. (57 years)	Wertheim's hysterectomy for endocervical adenocarcinoma (Stage I).	Normal	15 days	Lower end of left ureter.	Delayed excretion from the left kidney and well marked left pelvi-renal hydronephrosis. Right side normal.	Perfect continence of urine.	Left renal pelvis now within normal limits.
3.	Mrs. P.A. .. (42 years)	Wertheim's hysterectomy for anaplastic squamous cell carcinoma of the cervix (Stage II).	Normal	41 days	Lower end of right ureter.	Right sided hydro-ureter and hydronephrosis. Left side normal.	Continence of urine achieved.	Normal urinary tract.

anastomosed to the tube by a mucosa to mucosal suturing over a polythene catheter. The suture line was then buried beneath the flap of peritoneum once again extraperitoneal. An ordinary catheter was placed alongside the ureteric polythene catheter in order to drain the bladder.

The polythene catheter was removed on the third post-operative day and the bladder catheter on the 6th day. Prophylactic sulphatriad was administered to forestall infection.

Result

All the cases achieved continence of urine following this procedure. The intravenous pyelograms before and after the occurrence of the fistula and that following the Boari operation of Case 1 are reproduced (Figs. 2–4).

Discussion

This operation seems to be a very useful one for post-operative ureteric fistula. It is a practical method, and very suitable when the ureter is too short and hence the gap between it and the bladder is considerable. Ockerblad (1947) says that it does not matter at all in what way the bladder flap is created, where the base of the flap is located or in which direction the flap is fashioned. He, however, warns that the flap should not be too narrow, otherwise it would shrink and would thus invalidate the operation eventually. The blood supply to the anastomosis seems to be quite adequate.

Summary

Three cases of post-Wertheim uretero-vaginal fistula, who were treated by Boari operation, are reported. All patients achieved perfect urinary continence.

Acknowledgments

I wish to thank Mr. J. B. Blaikley, F.R.C.S. (Eng.), F.R.C.O.G., the supervisor of my work, for his advice and help, and to Mr. D. M. Wallace, *O.B.E.*, M.S., F.R.C.S.(Eng.), I extend my sincere gratitude for his encouragement and advice.

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INTRA-UTERINE AND EXTRA-UTERINE PREGNANCY COMBINED WITH OVARIAN CYST

BY

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COMBINED intra-uterine and extra-uterine pregnancy has been reported many times; Greenhill (1956) mentions records of 421 such cases. There are also several reports of ectopic pregnancy associated with ovarian cyst (Bowen, 1939; Zeratsky and McCanna, 1954; Gruneberg, 1958). However, in a search of the world literature over the last 40 years, we can only find references to 2 cases of intra- and extra-uterine pregnancy combined with ovarian cyst (Daltas, 1935; Ramos and Wernicke, 1942). The case described here, of a large pseudomucinous cystadenoma of the right ovary combined with a left tubal pregnancy and an intra-uterine pregnancy, which eventually went to term, must, therefore, be very rare.

CASE HISTORY

The patient, aged 26, and married 7 years, had had 2 normal pregnancies in 1954 and 1956, both ending in forceps delivery. She had had no previous significant illnesses.

She was seen at home by one of us (R.M.) early in August, 1959, complaining of attacks of central abdominal pain which radiated round to her back; she had also noticed a progressive swelling of her abdomen since June. She stated that her last menstrual period had commenced on 24th June, but that she had had some vaginal bleeding with clots in late July. Prior to this she had had a normal monthly cycle, menstruating for two days only. Examination revealed a softened cervix with a soft, globular swelling, about the size of an 18-week pregnancy, arising from the pelvis. A diagnosis of pregnancy indeed seemed likely, but, as the size of the swelling did not correspond to the period of amenorrhoea, an Aschheim-Zondek test was done. This was negative, but a repeat test 1 week later was weakly positive.

The patient was next seen on 2nd September. The swelling was 20 weeks in size. On vaginal examination the uterus could now be felt separately in a retroverted position, closely related anteriorly to a cystic mass; a diagnosis of ovarian cyst was made. A straight X-ray revealed an ill-defined, soft tissue mass rising from the pelvis, with no evidence of foetal parts. Admission was arranged for the following week for examination under anaesthesia and probable laparotomy, but the patient was admitted to hospital as an emergency early on the morning of 4th September, with a provisional diagnosis of torsion of an ovarian cyst.

On questioning (P.J.A.), it appeared that she had developed a particularly severe attack of central abdominal pain some hours before, again with radiation to the back. There had been no vomiting, intestinal or urinary upset, and no further vaginal bleeding since July; she now stated that this bleeding had commenced on the day that she had expected her menstrual period, and, although it had been heavier than usual with clots, it had lasted for the customary 2 days. Her general condition was good, with no signs of shock and her pulse, blood pressure and temperature were within normal limits; her haemoglobin was 85 per cent. The cardiovascular system was normal and the chest clear. There was an abdominal swelling of at least 20-weeks size, cystic and apparently rising from the pelvis; tenderness was marked over the upper part and a fluid thrill could be elicited. On examination *per vaginam* a retroverted, somewhat enlarged, softened uterus could be felt, with a smooth, closed cervix; anterior to the uterus was a cystic mass; there was marked tenderness in the right fornix, but no swelling or tenderness could be felt in the left fornix nor was there any suggestion of fullness in the pouch of Douglas.

The patient was taken to theatre later the same morning and examined under anaesthesia, when the above findings were confirmed. A laparotomy was therefore carried out (P.J.A., F.H.L.). On opening the abdomen, a large, multilocular ovarian cyst, about the size of a rugby football, was found, arising from the right adnexa. The uterus was lying behind this, retroverted and enlarged to about the size of an 8-week pregnancy. The cyst was delivered and removed intact; there was no evidence of torsion. On further examination of the left adnexa, clot was found to be extruding from the fimbrial end of the tube, which was markedly congested. The clot was squeezed out, but bleeding continued, and it was felt that the only wise course was to remove the left tube as well, and this was done. The left ovary contained a large, haemorrhagic corpus luteum which was left intact.

Pathological examination confirmed a pseudomucinous cystadenoma of the right ovary, with a thin, stretched right Fallopian tube attached. The left tube showed non-specific inflammatory changes; part of the clot expressed from it showed areas of syncytiotrophoblast.

Apart from a mild respiratory infection, convalescence was normal. In view of the findings at laparotomy, a further Aschheim-Zondek test was taken on 7th September, and this was positive. The patient was discharged on 19th September. She was next seen at the out-patient clinic on 3rd November, when she was feeling well. On examination her uterus was found to be anteverted, globular and enlarged to the size of a 16-week pregnancy. Her subsequent antenatal progress was normal and she had a spontaneous vertex delivery of a live female child, weighing 6 pounds 12 ounces, on 18th April, 1960. She attended the postnatal clinic on 9th June. A normal menstrual period had occurred in May. A retroversion of the uterus was corrected, but otherwise her pelvic organs felt normal, with no thickening present in either adnexa. She was last seen on 22nd September, 1960, when she was feeling well, with a normal menstrual cycle and healthy pelvic organs.

Summary

A case of left tubal abortion, associated with an early intra-uterine pregnancy and a pseudomucinous cystadenoma of the right ovary is reported. Treatment consisted of removal of the right tube and the ovarian cyst and left salpingectomy. The intra-uterine pregnancy went to term and resulted in the spontaneous vertex delivery of a live female child.

For permission to publish this case we wish to thank Dr. Hugh Stirling to whose wards the patient was admitted.

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SIR ARTHUR GEMMELL

Obituary

SIR ARTHUR GEMMELL

M.C., M.D., F.R.C.S.(Ed.), F.R.C.O.G., Hon.M.M.S.A.

SIR ARTHUR GEMMELL, born on 2nd November, 1892, died at his home in Liverpool on 24th September, 1960. He was educated at Uppingham School, King's College, Cambridge and Liverpool University. His undergraduate career, however, was interrupted by the 1914–18 War during which he served as a combatant, first in the Liverpool Scottish Regiment and later in the Queen's Own Cameron Highlanders. He was wounded at Ypres in 1915 and was later awarded the *M.C.* and the Greek Military Cross. Arthur Gemmell loved the army life so well, its organization and discipline, that he was tempted to remain a professional soldier. Indeed, even when he returned to complete his medical studies in the Clinical School of the University of Liverpool, he remained in the Territorials and commanded the Liverpool Scottish Regiment during the years 1923–27, holding the brevet of Colonel. Moreover, throughout his life he retained his interest in all military matters. The Second World War again saw Arthur Gemmell in uniform, as a captain in the *R.A.M.C.* Territorial Unit of the University of Liverpool. His duties consisted mainly in organizing the receipt and disposal of the wounded and, for this purpose, he spent many dark and cold nights on wayside stations, nights during which he should have been resting from the arduous demands of a busy obstetrical and gynaecological practice. For, by that time, Arthur Gemmell had followed in the footsteps of his father, the late Dr. J. E. Gemmell, who was himself a well-known Liverpool gynaecologist.

Arthur Gemmell qualified M.B., B.Chir. (Cambridge) in 1922, and subsequently obtained the M.A. and M.D. degrees of the same University. By 1924 he was a Fellow of the Royal College of Surgeons of Edinburgh, and within the next three years was appointed to the consultant staff of the Hospital for Women (Shaw Street), the Liverpool Maternity Hospital and the David Lewis Northern Hospital, Liverpool. These hospitals, as well as others in Wallasey, Ormskirk and Southport, Arthur Gemmell served with skill and conscientiousness, devoting meticulous, skilful and kindly care to every patient no matter how humble she might be. Everything he did was characterized by his capacities for attention to detail, for selfless devotion to a rigid sense of duty, for impartial judgment based on carefully ascertained facts, for suppression of personal feelings, for loyalty to his colleagues both senior and junior. Arthur Gemmell never completed an operation without himself writing or dictating a detailed record; he never chaired a committee or expressed an opinion without knowing every fact which might have a bearing on a problem. His many original articles, several of them published in this journal, are an example to any would-be writer. If their style is sometimes stilted they reveal an extraordinary factual and grammatical accuracy. They contain no statements which the author himself did not check and cross check, and no reference to the literature which he had not himself read.

Arthur Gemmell's ability and willingness to serve others brought him many administrative

responsibilities. He was a member of the Board of Governors of the United Liverpool Teaching Hospitals and of the Liverpool Regional Hospital Board. He was Chairman of the Obstetrical and Gynaecological Advisory Committee for the Liverpool Region. He was Honorary Treasurer of the Liverpool Medical Institution and President of the University Club. He was also President of the North of England Obstetrical and Gynaecological Society and of the Section of Obstetrics and Gynaecology of the Royal Society of Medicine. For many years he was the convener of the Gynaecological Visiting Society of Great Britain and Ireland. His resposibilities of this kind were legion and only a man of Arthur Gemmell's physical and moral fibre could have shouldered them. And he did so faithfully despite his allegiance first to his patients and secondly to the Royal College of Obstetricians and Gynaecologists.

Arthur Gemmell was a foundation member of the College and his membership of the Council and of its sub-committees extended over a continuous period of 16 years. He acted as Chairman of the Scientific Advisory Committee and of the Dominion Committee. As Honorary Treasurer he, in 1947, launched the first appeal for the money which ultimately made it possible to build the new College House. At all times he kept faith in this project and it is sad that his last illness prevented his attending the Opening Ceremony in July, 1960. Meanwhile, he had held the high office of President and had opened the first College House of the Australian Regional Council. As his responsibilities mounted, so did his distinctions. In Australia he gave the Arthur Wilson and Blackham Memorial lectures; in the United States of America he was made an honorary member of the American Gynecological Society, the American Gynecological Club and the New Orleans Obstetrical and Gynecological Society; at home he received a knighthood, was made an Honorary Fellow of the Edinburgh Obstetrical Society and was admitted to the Honorary Mastership in Midwifery of the Society of Apothecaries.

At the height of his career, and at a time when he had so many cares and responsibilities, his wife Gladys developed a serious illness which ultimately caused her death in 1957. At a time when he most needed her help, Arthur Gemmell became her nurse through many years of invalidism. His loyalty, kindness and love for her remained undimmed and whenever duties elsewhere could be escaped he would be found at her bedside. No one seeing him in hospital or committee at this time could guess the strain under which he lived and worked. To a lesser man it would have been intolerable. For Arthur Gemmell was a great man, as only those who worked close to him could know. One of the signs of his greatness was humility. He never realized his own great qualities and all his honours were thrust upon him. And despite these honours he remained a modest and unassuming man, ready to help even his juniors. As head of the department of Obstetrics and Gynaecology in the University of Liverpool, I, who was very much his junior, had Arthur Gemmell as my Senior Lecturer. Anyone else would have resented the trick of fate which reversed our natural roles but not Arthur Gemmell. He, more than any other, helped to smooth the way for a new Professor and the establishment of a whole-time Unit.

He was a man who spent his whole life in the service of his family, his patients, his country, the medical services, his University and its students, and not least the Royal College of Obstetricians and Gynaecologists. He had little time for leisure but this did not concern him; he was most happy when serving his fellow men and a good cause.

Arthur Gemmell is survived by two daughters and one son who have every reason to be proud of their father.

T. N. A. JEFFCOATE

REPORTS OF SOCIETIES

GLASGOW OBSTETRICAL AND GYNAECOLOGICAL SOCIETY

October 1960

A combined meeting of the Glasgow Obstetrical and Gynaecological Society and the Birmingham and Midland Obstetrical Society was held in Glasgow, in the Rooms of The Royal Faculty of Physicians and Surgeons, on 7th October, 1960.

The Presidents of the Societies, Mr. Samuel Davidson (Birmingham) and Professor D. F. Anderson (Glasgow), presided. The subject for discussion was

Some Aspects of Pelvic Floor Repair

Dr. Wallace Barr and Dr. M. L. Paterson described their investigation of

Urinary Infection After Colporrhaphy

Dr. Barr said they had found that, unless precautions were taken, the urinary infection rate could be somewhere in the region of 90 per cent after colporrhaphy. This infection rate was greatly reduced by alterations in catheterization technique and by the instillation of chlorhexidine into the bladder after each catheterization.

A series of 352 patients was studied and they were followed up for between 1 and 3 years after operation. Nearly all had amputation of the cervix carried out and some attempt made to restore the urethro-vesical angle. Seventy-three of the 352 patients had urinary symptoms at the first follow-up examination 8 to 10 weeks post-operatively. He emphasized the necessity for a careful interrogation technique in eliciting an accurate history of abnormalities of bladder function. All of the 73 had a catheter specimen of urine examined and in 21 of these a definite infection was found. Treatment of the infection in the latter group resulted in disappearance of the symptoms in 18 cases.

This left 55 still with symptoms. They were all sent for urological investigation in which cystoscopy and intravenous pyelography was carried out, the urine was re-examined, and the bladder capacity estimated. In 26 of these some abnormality was found, either a trigonitis, chronic interstitial cystitis or a small capacity bladder. Treatment was with Bellergal, Probanthine, or one of the newer sulphonamides such as Midicel or Lederkyn. Of these 26 cases, 16 slowly improved and by the end of a period of up to a year were finally pronounced cured.

This left a hard core of 39 cases who at the end of a year were still having symptoms. An additional 5 cases who were initially well after operation developed urinary symptoms subsequently. These 44 cases, 12·5 per cent of the series, were regarded as failures.

Dr. Paterson discussed these failures and classified them broadly into three groups: 8 patients who exhibited symptoms of "bladder neurosis", 10 patients who made up an infective group and 26 patients where the failure was anatomical. The "bladder neurosis" group related their symptoms with relish and tended to resist further investigation. Where investigation was permitted, no abnormality was found by cystography, cystoscopy and cystometry or on examination of the urine. He suggested that these failures could be prevented by better pre-operative screening and that social and psychiatric investigation would be more beneficial than surgery.

The 10 infective failures included one case of tuberculous cystitis. In the others trigonitis or interstitial cystitis was found. The causation of the infection was discussed and he claimed that, since the abandonment of the in-dwelling catheter and substitution of routine instillation of chlorhexidine solution after each catheterization, this type of failure had been almost eliminated.

The 26 anatomical failures included 11 cases where anterior vaginal wall laxity persisted and in these further operation had been successful. Eleven cases had demonstrable stress incontinence and here stress cystography had proved of very limited usefulness. Cystoscopy was considered to be more valuable and the uniformly satisfactory results following the Marshall-Marchetti operation in these cases was held to support this view. In the remaining 4 cases the failure was due to antero-lateral scar crescents drawing the bladder base posteriorly. The treatment of this condition had proved to be difficult and lengthy.

Mr. Henry Roberts read a paper on

Stress Incontinence—A Re-evaluation

He emphasized the necessity for strictly controlled conditions in cystography and then reviewed his findings. Radiographs in the normal woman usually show a well-defined angle between the urethra and bladder base both at ease and straining and this angle disappears during micturition when the bladder base and upper urethra assume a straight line. In prolapse without stress incontinence the main area of descent is behind Mercier's inter-ureteric bar and regardless of the extent of rotation of the bladder and upper urethra around the triangular ligament, the posterior urethro-vesical angle remains normal both at ease and on straining. When stress incontinence is present the area of descent is in the sensitive area in front of Mercier's bar which results in

loss of the posterior urethro-vesical angle in 90 per cent of cases. On straining, funnelling of the urethro-vesical junction occurs in 50 per cent of cases and leakage into the upper urethra in the worst cases amounting to 25 per cent of those examined. These changes resemble the appearances during micturition except that they occur at ease or on straining without evidence of detrusor contraction.

Nearly 80 years ago Professor Le Gros Clarke indicated that the hydrostatic pressure within the bladder is 250 times the force required to control the neck. Furthermore, it seems that this relatively small force is minimal when the relationship of urethra to bladder is perpendicular and maximal when it is tangential. Controversy exists over the interpretation of the anatomical changes largely because of failure to give adequate consideration to the variability of the physical stress to which the urethra is subjected. In the relaxed state the bladder transmits increases of intra-abdominal pressure without modification and the pressures can be recorded through a catheter. The speaker had found that at rest the intra-abdominal pressure values vary with the position of the subject:

Lying down	..	9 to 10 cm. of water.
Sitting ..	..	20 to 40 cm. of water.
Standing	..	46 to 60 cm. of water.

Walking produces small but sudden increments in these values. Coughing and straining may produce high pressures, the figures ranging from 50 to 250 cm. of water. In stress incontinence leakage may occur with a sudden small increase in pressure as in coughing, walking or jerking, whereas the same patient may remain continent during gradual straining to produce pressures three times as great. In the former circumstance the compressor urethrae is caught "unawares" whereas the latter allows time for mobilization and reinforcement of the urethra. Until recently it was his belief that heavy lifting caused an appreciable increase in intra-abdominal pressure but his experiments had failed to show such a rise in pressure. He had found that the strain is normally taken entirely by the arms, back and legs and only transmitted to the abdominal cavity when a corset is worn. He therefore considered the garment likely to be a factor in causation or aggravation of prolapse and stress incontinence.

Choice of treatment is occasionally difficult. There are over 100 possible methods but few gynaecologists utilize more than three or four. Physiotherapy, with Faradism or the use of a perineometer seems worthy of trial in mild cases especially after pregnancy. Vaginal repairs with urethral buttress may cure approximately 80 per cent. Lateral dissection must be adequate and should extend until the venous plexus of Santorini is exposed to allow adequate plication of the bladder neck and upper urethra and reinforcement with pubo-cervical fascia. Marchetti operations are often performed in favourable cases as a part of a planned abdominal procedure whereas sling operations are usually restricted to recurrent and severe cases without prolapse, yet the results of the latter are more durable and reliable.

Mr. Roberts recommended two years as a reliable "time test" of success. Few patients escaped two winters without a common cold which would subject the urethra to coughing pressures of 150 to 200 cm. of water. The fact that the maximal coughing pressure for some weeks after operation was only half the pre-operative figure explained the temporary improvement so commonly found soon after operations which ultimately failed. He had examined 100 vaginal repairs with urethral buttress two years after operation and 19 of the patients had persistence of symptoms. He advocated a closer study of all severe and recurrent stress incontinence and suggested that cystography (with manometric control) and simple cystometry in the hands of an expert would amply repay the time expended.

Dr. Robin Murdoch spoke on

MARITAL FUNCTION FOLLOWING REPAIR OPERATION

He said that judging by the number of contributions to the medical literature, it would appear that within the last twenty years more consideration has been given by gynaecologists to the effect of the repair operations on marital function. There is now less embarrassment on the part of both patient and gynaecologist in discussing the question of marital relations after plastic operation. We have become increasingly aware that should the operation result in dyspareunia a marriage may be ruined. Brutar, in an analysis of 147 patients complaining of dyspareunia, made this particular point.

It is the duty of the gynaecologist to ensure that in repairing a prolapse, he restores the vagina as nearly as possible to the size and shape which existed at marriage and he should discuss the operation with the patient and make her aware that continuation of marital relations should be normal.

In the last two decades there have been several notable contributions on the results from plastic repair operations. Stallworthy found that 25 per cent of all patients complained of dyspareunia after operation but this was permanent in only 10 per cent. Solomons found a 14 per cent occurrence in 69 patients; Gibson 10 per cent, Brutar 20 per cent and Jeffcoate 30 per cent. As a result of this high figure, Jeffcoate advocates that the incidence of dyspareunia would be considerably reduced if colpo-perineorrhaphy ceased to be a routine part of the operation and was only carried out if there was a clear indication for it.

He enumerated the causes of dyspareunia after repair operation as follows:

(1) Narrowing of the vaginal canal due to the removal of too much mucosa or to the underlying fascia and muscle being stitched too tightly. There would be fewer cases of dyspareunia and apareunia if the introitus was left wide enough to admit three fingers at the end of the operation.

(2) Abnormal angulation of the vagina due to excessive rebuilding of the perineum especially where it consists of skin and hypersensitive scar tissue with no adequate perineal muscle.

(3) Shortening of the vagina due to cross union between the anterior and posterior walls in the line of the sutures. These can usually be broken down by the finger and recurrence can be prevented by the use of Dienoestrol Cream. If this is neglected permanent dyspareunia or apareunia would result.

(4) Atrophic or infective vaginitis, granulation tissue at the wound edges resulting from mal-approximation, and portions of non-absorbable suture left in the perineum may all cause dyspareunia.

(5) Deep dyspareunia may result from failure to correct a retroversion or prolapse of ovaries.

The speaker then discussed the results in 100 patients on whom he had operated personally in the past five years. The ages of the patients ranged from 27 to 66 years. In 17 cases the post repair was omitted. Eleven of the patients complained of dyspareunia and two of these had responded successfully to treatment with Dienoestrol Cream while a further 3 were still being treated. Ten of the patients had made no attempt at coitus for various reasons, mainly because they were afraid of causing damage. Two of these after reassurance subsequently reported that there was no difficulty.

In conclusion he said that in order to assess the success or otherwise of a repair operation it may be necessary for the patient to report for interview and examination for up to one year post-operatively.

BOOK REVIEWS

"Clinical Obstetrics and Gynecology." Vol. 4, No. 1. "Symposia on Obstetric Anaesthesia and Analgesia, and on Vaginal Surgery." March, 1961. Hoeber, New York.

THE current number of this quarterly-in-book-form is devoted to methods of anaesthesia and analgesia in labour and to facets of vaginal surgery, but there is also a sting in the tail in the shape of a special article on the medico-legal aspects of psychogenic abortion. This well-referenced paper is a stimulating and entertaining combination of erudition and scepticism.

The contributors to the symposium on anaesthesia are all from the Western Reserve University, Cleveland, Ohio, marshalled by that redoubtable figure, Dr. Robert A. Hingson. Not surprisingly there is considerable emphasis on conduction anaesthesia but not unduly so. Taking into account the different structure of the maternity services in Britain, the chapter most likely to receive close attention here is that on "Uterine Dynamics" (by Kretchmer and Vasicka), for it includes a lucid summary of much recent research into uterine physiology.

The section on vaginal surgery, which is edited by Dr. A. A. Lash, is naturally less comprehensive, yet it stretches to include an account of operations for double uterus. The Manchester repair is championed by Robert Gordon, and E. G. Waters contributes a forceful chapter on enterocele and its cure. The sole offering from this side of the Atlantic is a short essay by Stanley Way on operations on the vulva.

S. Bender

"Gynaecological Urology." Edited by ABDEL YOUSSEF. Pp. 826. Charles C. Thomas, Springfield, Illinois, 1960. Distributed by Blackwell Scientific Publications Ltd., Oxford. Price £9.

THIS book is a comprehensive presentation of the urological aspects of obstetrics and gynaecology by 32 contributors of international eminence. The scope ranges from the historical to the experimental. Introductory chapters deal with embryology, anatomy and physiology. The effects of pregnancy and gynaecological conditions on the urinary system are fully discussed. A new concept of pyelitis of pregnancy is presented. There are excellent sections on the prevention and treatment of urinary tract injuries during obstetrical and gynaecological operations and on the avoidance of post-operative infections.

Other chapters deal with urological affections of gynaecological significance. There are modern opinions on urinary diversion and the treatment of acute anuria. Provision is made for an international clientele with extensive descriptions of genito-urinary fistulae, calculus disease and schistosomiasis. The chapters describing the operative treatment of urinary fistulae following radiotherapy are worthy of special mention.

The effect of drugs on the bladder and its internal sphincter is presented by the editor. Elsewhere he makes a strong plea for abandonment of Sir Eardley Holland's term "stress incontinence of urine" in favour of "sphincter incontinence of urine". He also describes the uncommon but interesting syndrome of "menouria" due to utero-vesical fistula above the level of the internal os.

The selection of contributors is well balanced but the detail with which each has presented his favourite subject shows considerable variation. There is also overlap, and even conflict, of views between one contribution and another. Latzko's method of treating vesico-vaginal fistulae by partial colpocleisis could have received greater emphasis. This book has much to offer the urologically minded obstetrician and gynaecologist and is well produced except for the reproduction of radiographs.

"Frau und Sport." By PROFESSOR E. J. KLAUS (Münster) and PROFESSOR H. NOACK (Bielefeld). Pp. viii+156, with 56 illustrations and 51 tables. Georg Thieme Verlag, Stuttgart, 1961. Price D.M.19.80.

A SPECIALIST in the medical problems of athletes and a gynaecologist have collaborated to prepare this monograph, which summarizes the extent of our knowledge concerning the effects of physical exertion on women. The first chapter relates body constitution to athletic achievement. The second chapter is devoted to injuries and pathological states resulting from physical exertion. The authors consider that amenorrhoea, menstrual irregularities and the onset of dysmenorrhoea may be the first sign of strain and over-exertion, the consequence of bad training. They regard athletes as good obstetric subjects; they have not found any evidence to support Sellheim's observation that sportswomen have prolonged and inert labours, although they have observed that the incidence of perineal damage is greater in athletes. There follows a chapter on the maintenance of health and the prevention of injuries. The final chapter deals with female physiology and its relation to physical activity. Some interesting figures are presented to show that women are strongest, possess greater endurance, co-ordinate better, and produce their best athletic performances in the post-menstrual phase. Performance is not as good as after, but better during menstruation than in the pre-menstrual phase. From a series of animal experiments the authors claim to have related these observations to the presence of oestrogens, which facilitate adaptation to

stress. The athletic performance of many women improves after pregnancy. This monograph provides an interesting review and reference work to a neglected subject.

Peter J. Huntingford

"Die präoperative Röntgenbestrahlung des Mammakarzinoms." By E. MUNTEAN (Graz). Pp. iv+108, with 9 illustrations and 26 tables. Georg Thieme Verlag, Stuttgart, 1961. Price D.M.17.50.

IN this monograph the problem of the treatment of breast cancer is reviewed, with particular reference to the place and timing of radiotherapy. The author reports the results of pre-operative irradiation of 139 patients with carcinoma of the breast. He concludes that inoperable cases can be made suitable for surgery; in only a very small proportion of cases is radiotherapy alone sufficient; the number of early recurrences is less when pre-operative radiotherapy is used; pre-operative radiotherapy is the treatment of choice for advanced cases. Most of the work is devoted to a review of the literature; it contains 880 references.

Peter J. Huntingford

"Die Intersexualität." Edited by PROFESSOR C. OVERZIER, with contributions by M. L. Barr (London, Canada), J. R. Bierich (Hamburg), W. M. Davidson (London, England), C. E. Ford (Harwell), H. Gelbke, (Göttingen), R. Hasche-Klünder (Hanover), G. A. Hauser (Basle), H. D. Henning (Cologne), K. Hoffmann (Mainz), W. Koch (Munich), B. Lennox (Glasgow), J. M. Opitz (Iowa City), C. Overzier (Mainz), J. H. Schultz (Berlin), D. R. Smith (Reading), M. Watzka (Mainz), E. Witschi (Iowa City) and J. Zander (Cologne). Pp. xvi+560, with 193 illustrations and 38 tables. Georg Thieme Verlag, Stuttgart, 1961. Price D.M.119.

AT first sight the reader shies at reading a book of this length on such a specialized subject as intersex. Nevertheless the reviewer found this book enthralling and very instructive. As the editor suggests in his preface, cases of intersex may be met with by workers in almost any branch of medicine; its problems involve several different specialities and it is therefore of universal interest.

This work aims to be comprehensive and to cover every aspect of the subject in detail: thus it includes chapters on the development of the genital tract, the aetiology and embryogenesis of intersexual anomalies, comparative veterinary pathology, sex chromatin, nuclear sex, the nuclear sex of tumours, chromosomal abnormalities, and hormones (this chapter contains a very good review of the physiology of steroid hormones, methods for their estimation, and their alteration in disease). In addition there are detailed expositions of the main clinical types of intersex. There is a precise description of the plastic surgical operations used for the correction of intersexual anomalies. Each chapter is complete in itself and is written by an expert in his own field. It is remarkable that each author has contrived to present his subject so that it is readily understood by the uninitiated, but at the same time presents a complete and up-to-date review for the expert. Many of the references quoted are from 1960. The index of authors provides an easy way of locating references and comments on them in the text.

The book is beautifully produced with a large number of clinical photographs, microphotographs and tables; many of the latter provide a complete and concise summary of all the case reports of particular anomalies that have been recorded in the literature.

Peter J. Huntingford

"Information, Please! For Women Only." By ALFRED DREYFUS II. Pp. 556; 10 diagrams. The Dunhill Chart. Vantage Press, New York, 1961. Price $7.50.

THE author states that his purpose in writing is "to give helpful private counsel about some of the things women have always wanted to know with more certitude".

There is indeed much detailed information given and even a glossary of medical terms is included. Pregnancy and sexual problems are dealt with fully and clearly and the advice given should be of great value to many women. The description of the aetiology of headache and backache includes the rarest causes, and the sections on menstruation and leucorrhoea are somewhat confusing. The unfortunate impression is given that syphilis and gonorrhoea are the commonest diseases in the U.S.A. Of limited value to readers in this country is a comprehensive tabulation of the complicated sex laws of each American state.

More than two-thirds of the printed pages are devoted to a series of repetitive charts demonstrating the weekly progress of pregnancy through its full ten months, allowing for conception occurring on every day of the year with the exception of 29th February, an insult to the intelligence of most women.

Description of the rhythm method of contraception with explanation of the Dunhill Charts gives an over-optimistic picture of its safety, while other methods of birth control are unfairly dismissed in a few paragraphs.

A layman has succeeded in answering a wide range of questions which confront and trouble women, but in some respects the provision of excessive detail may only serve to confuse and mislead.

Barbara Law

"Atlas of Obstetric Technic." By J. ROBERT WILLSON, M.D., M.S. Pp. 304, with 55 plates. The C. V. Mosby Company, St. Louis; Henry Kimpton, London, 1961. Price 93*s.* 6*d.*

THIS atlas is designed to provide the detailed description of operative procedures which is usually not included in standard obstetric textbooks. It has been prepared specifically as a guide to technique for the use of those in training, the general practitioner-obstetrician and the general surgeon faced with the occasional necessity of conducting an operative delivery. The introductory chapters deal with staff organization, delivery room

facilities and the conduct of normal labour. Efficient planning in regard to both personnel and physical facilities is stressed and much useful information is provided. Few, if any, manipulations are omitted and each is described step by step. Black and white diagrams appear on the right-hand page with a verbal description, for the most part brief, opposite. About one-third of the whole book is devoted to forceps extraction, this chapter beginning with some helpful comments on indications, requirements, design of the instruments and types of forceps delivery. Some ambiguity is evident in the author's distinction between low and outlet forceps for he himself notes that the former is also designated low mid-forceps while the latter is also called low forceps. The need to describe in equal detail both right and left anterior, transverse and posterior occiput positions is questionable. The registrar in training might well, however, profitably pursue his way through this section with the use of a doll and pelvis. It is worth while noting that, despite the transatlantic origin of the book, there is no point of principle and very few of detail contrary to current British practice. One might prefer transverse lie or shoulder presentation to the author's use of transverse presentation.

The sentences are short and the style staccato, but every paragraph conveys an exact and unequivocal meaning. Although the obstetric specialist may learn nothing new from a perusal of Professor Willson's work, he will without doubt be impressed by the soundness of his approach, the clarity of the illustrations and above all by the lucidity of his writing. This atlas might with benefit be made available in every labour ward.

James G. Lawson

REVIEW OF CURRENT LITERATURE

CONTENTS

	REF.
PHYSIOLOGY	163
PREGNANCY	165
LABOUR	178
OBSTETRIC OPERATIONS	188
LACTATION	192
INFANT	193
GYNAECOLOGY	
Disorders of Function	195
Infections of the Reproductive Organs	200
New Growths of the Reproductive Organs	203
Operations	217
Urology	226

PHYSIOLOGY

163. **Further Studies of the Cation Concentration of Human Uterine Muscle by Means of Micro-Analytical Methods.** (Weitere Untersuchungen zum Kationen-Gehalt der menschlichen Uterusmuskulatur unter Anwendung mikroanalytischer Methoden.)

By K. CRFTIUS and K. BEYERMANN. *Zbl. Gynäk.*, **83**, 165–186. Feb. 4, 1961. 8 tables. 95 refs.

The authors begin their report with a fairly detailed review of work done by others in this field. This brings the reader up to date with recent advances in the biochemistry of uterine musculature. Their own investigations were carried out on biopsy material obtained from 39 uteri of which 17 derived from pregnant women at term. They also studied biopsies of skeletal musculature of non-pregnant women for comparison. The potassium, sodium, calcium and magnesium concentration was assayed per 100 g. of dry weight.

The corpus of non-pregnant women of child-bearing age was found to have a higher sodium and a lower potassium concentration than skeletal musculature, with an average of 895 mg. of potassium, 745 mg. of sodium, 45·4 mg. of calcium and 53·2 mg. of magnesium. The values for calcium were twice as high as they were in striped muscle, whereas those for magnesium were lower. In the case of the cervix, mean values for potassium were 481 mg. which is lower than in the corpus, the sodium and calcium levels did not differ significantly, but those for magnesium were 35·9 mg. per cent, i.e., lower than in the corpus. The difference between electrolyte concentration of cervix and corpus are attributed to the higher proportion of connective tissue in the cervix with comparative reduction of the intra-cellular compartment.

In menopausal uteri, the potassium level is lower (653 mg.) but the sodium levels higher (826 mg.) in the corpus than during reproductive life. The calcium levels rise with advancing age, whereas the figures for magnesium are well below those of reproductive life (43·2 mg.). These findings are thought to be related to fibrosis associated with a rise in extra-cellular cations.

In pregnant women at term, the corpus showed a rise in all four electrolytes as well as in water content.

No significant difference was found before and after the onset of labour. Comparison between corpus and cervix showed that the potassium level was lower, the sodium possibly higher, calcium equally high, but the magnesium concentration lower in the cervix.

Bruce Eton

164. **Histochemical Demonstration of 3-Beta-ol-Steroiddehydrogenase Activity in the Tissues of Endocrine Organs.** (Über den histochemischen Nachweis der 3β-ol-Steroiddehydrogenase-Aktivitat in Geweben endokriner Organe.)

By K. FUHRMANN. *Zbl. Gynäk.*, **83**, 565–572, Apr. 15, 1961. 1 table. 5 figs. 28 refs.

In recent years the problem of synthesis of steroid hormones in endocrine glands has acquired major interest with particular reference to the enzyme systems responsible for it.

The author describes the results of his histochemical

study of endocrine glands after incubating tissue slices with suitable hormone substrates. The histochemical colour reaction showed the presence of 3-beta-oldehydrogenases. He demonstrated that pregnenolone is reduced to progesterone and dehydroepienandrosterone to androstenedione.

His investigations support the view that the initial steps in the biosynthesis of steroid hormones appear to be identical in adrenal cortex, ovary, testis and placenta, accounting for the stages of acetate → cholesterol → androgens → oestrogens. The predominance of one or other hormone in the various glands under physiological conditions would thus be mainly a quantitative task of the corresponding enzyme systems. *Bruce Eton*

PREGNANCY

165. **The Carbon Dioxide Tension of the Amniotic Fluid.**

By S. SJÖSTEDT, G. ROOTH and F. CALIGARA. *Amer. J. Obstet. Gynec.*, **81**, 1–3, Jan. 1961. 1 table. 2 figs. 9 refs.

The carbon dioxide tension of the liquor amnii is an indication of the intra-uterine oxygenation of the foetus. If the foetus suffers from hypoxia because of deficient oxygen transportation from the mother across the placenta or reduced circulation in the infant carbon dioxide will accumulate and by diffusing into the amniotic fluid will cause increased carbon dioxide tension. The authors estimated carbon dioxide tension in samples of liquor amnii taken from 27 women at or near term, and from 23 women undergoing legal abortion in early pregnancy. The mean carbon dioxide tension in early pregnancy was 50·9 mm. Hg, and in late pregnancy 57·3, a difference of 6·4 mm. Hg. The condition may be compared to a respiratory acidosis in adults where there is a hypoxia and a hypercapnia. *F. J. Browne*

166. **Menarche and Pregnancy.** (Menarche und Schwangerschaft.)

By M. FÖLLMER. *Arch. Gynäk.*, **194**, 355–364, 1961. 3 tables. 6 refs.

Mikulicz-Radecki and Kausch published a paper in 1935 on this subject in which they reached the conclusion that there seemed to be a period of several years' physiological sterility following the menarche; they explained this finding by postulating the occurrence of anovulatory cycles. The author who lives in Libya doubted the reliability of this paper and, therefore, re-investigated the problem. He questioned 100 unselected fertile Arab women from the lower and middle social classes as to the time of menarche, the time of marriage and the interval between marriage and childbirth. Almost one-third of these women had been married before the menarche and about one-half of the remaining women were married in the first year after the menarche. Pregnancy occurred within the first year in 78·6 per cent of the girls married before the menarche (in 71·4 per cent within the first six months). A high proportion of these girls conceived after the first menstrual period and one girl became pregnant even before she had ever menstruated. Of the 68 women who got married after the menarche 86·4 per cent conceived during the first year of marriage.

The author concludes from these figures that there is no physiological sterility following the menarche in the Arab woman, whom he does not regard as sexually more mature than the European woman. With regard to the question whether pregnancy in such very young girls, presumably with small hypoplastic uteri, progresses to term, Professor Föllmer states that the size of the uterus is unimportant for the fate of the pregnancy, the decisive factors being the functional abilities of the ovaries and the placenta. 89 per cent of the pregnancies ensuing in the first two years of marriage progressed to term.

Erica Wachtel

167. **Urinary Estriol as an Index of Placental Function.**

By J. W. GREENE, J. C. TOUCHSTONE and H. FIELDS. *Obstet. and Gynec.*, **17**, 349–354, Mar. 1961. 4 figs. 13 refs.

In normal pregnancy there is a progressive rise in urinary oestriol excretion after the seventh week, and a tremendous increase occurs from the sixteenth week until term. The authors, using a chemical method of oestriol assay in a 24-hour specimen of urine, show that when placental function is inadequate the oestriol production is reduced, so that the method seems useful in predicting the outcome of abnormal bleeding and questionable foetal viability. Placental dysfunction and certain abnormalities of pregnancy are reflected in oestriol excretion levels. *J. G. Dumoulin*

168. **Alkaline Phosphatase Activity in Granular Leukocytes as a Test for Early Pregnancy.**

By W. B. HAVER and H. J. QUIGLEY. *Obstet. and Gynec.*, **17**, 238–242, Feb. 1961. 5 refs.

Activity of alkaline phosphatase in mature granular leucocytes, measured quantitatively by a cytochemical method, has been tested in diagnosis of early pregnancy by the authors in 119 women. All cases were less than 70 days from the onset of the last menstrual period. Prepared slides of peripheral blood smears were examined under oil immersion, the amount of brown staining in the cytoplasm being proportional to the level of alkaline phosphatase activity.

There were a few equivocal results needing repeat tests, but of the 70 pregnant cases a correct diagnosis was reached in all, and of the 47 non-pregnant cases the accuracy of diagnosis was 87 per cent. Thus, the test may provide a rapid and inexpensive answer in diagnosing pregnancy. *J. G. Dumoulin*

169. **Accurate Early Detection of Cyesis: Re-evaluation of the Rat Test.**

By J. R. BETSON and B. B. LONGWELL. *Obstet. and Gynec.*, **17**, 234–237, Feb. 1961. 2 tables. 22 refs.

This paper concerns the evaluation of the rat pregnancy

test. In it 2 ml. of filtered urine are injected intraperitoneally into 2 immature, albino, female rats. Hyperaemia of the ovaries is looked for in one rat at 6 hours and the other at 24 hours. In the series there were 593 double positive tests and 534 double negative. Seventeen rats died from toxic effects. In the positive group the accuracy of diagnosis was 100 per cent; whilst in the negative group there were 4·5 per cent inaccurate results. Some of the false negatives were due to too early collection of specimens (before the fortieth day of gestation). Sixteen of the patients with false negative results aborted 2–14 days after the test. The test can therefore be used with confidence. *J. G. Dumoulin*

170. **Management of Cases of Abortion.**

By W. S. E. Perera. *Brit. med. J.*, **1**, 705–707, Mar. 11, 1961. 15 refs.

Among the disadvantages of having to admit large numbers of cases of abortion to a Gynaecological Ward is the blocking of a variable number of beds making arrangements of clinic admissions difficult.

In 1950 an abortion unit with 40 beds was made available at Walton Hospital, Liverpool, and this paper is a review of the work in that Unit during the years 1958 and 1959. A total of 2,387 cases of abortion were admitted and of these 1,450 (62 per cent) were inevitable or incomplete. 643 cases of threatened abortion were diagnosed and in 72 per cent of these pregnancy continued. It was sometimes difficult to differentiate between threatened, incomplete and complete abortions.

In cases of threatened abortion, favourable results were achieved with bed rest and sedation, and the impression was gained that the administration of large doses of hormones is not justified.

If the abortion was found to be inevitable or incomplete, any products of conception in the cervical canal were removed digitally or with sponge forceps and ergometrine mg. 1 was given intramuscularly. Except for cases requiring emergency treatment, surgical evacuation was subsequently carried out on one of the three operating sessions held each week and the patient was discharged from hospital on the fourth day after operation. A sharp, rather than a blunt curette, is used. Intra-uterine packs and douches were not used.

Intervention has a great advantage over non-intervention, in that the average length of stay of each patient in hospital is much reduced. The dangers have been greatly reduced by the introduction of antibiotics and an efficient blood transfusion service. For similar reasons active treatment is advocated in cases of septic abortion.

High concentration pitocin drips have proved to be valuable in cases of missed abortion.

If transfusion is required, then plasma or blood is preferred to dextran which may cause defibrination.

A mortality of 0·06 per cent was achieved.

It is suggested that the greater use of the "flying squad" and the provision of more beds, preferably in special units, would result in a reduction of the national mortality figures in cases of abortion. *R. W. Grayburn*

171. **Renal Function in Normal Pregnancy and in Toxaemia of Pregnancy.** (Die Nierenfunktion in der normalen Schwangerschaft und bei Schwangerschaftstoxikosen.)

By V. Friedberg. *Geburtsh. u. Frauenheilk.*, **21**, 333–344, Apr. 1961. 5 figs. 1 table. 58 refs.

The author reviews the literature concerning the histological changes to be found in the kidney in association with toxaemia of pregnancy. He compares the findings of older workers using post-mortem material with those obtained by examination of biopsy material from living patients. In renal biopsies from normal patients in late pregnancy the author found no changes; but in pre-eclampsia there was reduction of the capillary lumen, clumping of the glomerular tuft, and narrowing of the capsular space. In 10 per cent of the author's cases there were sclerotic changes in the vessels, which he believes were indicative of pre-existing vascular disease. In eclampsia the changes were often very slight: in the early stages there was a deficiency of red cells, presumably due to spasm of the efferent arterioles; later the changes found in pre-eclampsia also occurred together with inclusion vacuoles in the tubular epithelium. Most of these changes disappeared within a few days of delivery.

The clearance values for inulin and para-amino hippuric acid were estimated three or four times during pregnancy in 12 patients. It was found that there was a 10 per cent increase in renal plasma flow and glomerular filtration rate in the early months of pregnancy, which was maintained until 32 weeks and thereafter slowly fell, until normal values were reached just before delivery. Almost identical results were obtained in mild cases of pre-eclampsia, but in severe pre-eclampsia and eclampsia there was a considerable reduction in renal blood flow and glomerular filtration rate; normal values were regained very quickly after delivery. In 48 women who had had toxaemia and who were seen several months post-partum there were only 8 with permanently reduced renal clearance rates. Renal biopsies were obtained from 5 of these women: in 3 there was vascular sclerosis, indicative of pre-existing essential hypertension; in 1 there was pyelonephritis; and in the fifth patient there were signs of tubular insufficiency, presumably the consequence of very severe eclampsia.

[This important paper correlates the findings of renal biopsy with renal function during normal and toxaemic pregnancies, and also after delivery. Its value, however, is reduced by the manner in which the material and results are presented.] *Peter J. Huntingford*

172. **Renal Lesions in Pregnancy.**

By J. Hopper, M. G. Farquhar, H. Yamauchi, H. D. Moon and E. W. Page. *Obstet. and Gynec.*, **17**, 271–293, Mar. 1961. 13 figs. 42 refs.

Percutaneous renal biopsies were performed in 7 pregnant patients and sections were studied by light and electron microscopy. One case developed a nephrotic state during pregnancy, one had chronic glomerulonephritis, one later developed disseminated lupus

erythematosus and one was a case of diabetic glomerulosclerosis. The authors were thus able to demonstrate an interesting selection of renal biopsies and they give some excellent photomicrographs.

By light microscopy, glomeruli from patients with pre-eclampsia were ischaemic, bloodless and swollen, and contained fibrinoid deposits. The electron microscope showed that the ischaemia was due to occlusion of the capillary lumen by swelling of the endothelium. The fibrinoid was deposited between the basement membrane and endothelium or between the endothelial cells. In post-partum biopsy material, the endothelial swelling had subsided and the fibrinoid deposits were minimal. In addition, large dense masses were seen within the endothelial cytoplasm, suggesting that the fibrinoid was removed from the glomerular capillary by the endothelium.

These changes were compared with those in pregnant patients with other renal diseases. No glomerular reaction was specific for any single disease, but one process or combination of processes predominated in each disease.

J. G. Dumoulin

173. **Heart Disease in Pregnancy.**

By M. B. E. SWEET. *S. Afr. med. J.*, **35**, 87–91, Feb. 4, 1961.

The author, a medical student, has reviewed 284 cases which were treated at the Maternity Hospitals under the aegis of the University of Cape Town. The incidence of heart disease was a little over 1 per cent and the commonest age group was 20–24 years. Rheumatic heart disease was responsible for 89 per cent of cases, congenital heart disease for 4·6 per cent and hypertensive heart disease for 3·9 per cent.

The importance of antenatal care is stressed. The maternal mortality was twice as high in non-booked cases. In addition both stillbirth and neonatal death rates were more than three times as high in this group. At delivery 7·15 per cent of booked cases were in grades 3–4 whereas in non-booked cases the corresponding figure was 20·8 per cent.

Management of labour and the puerperium is discussed as well as indications for termination. Hysterotomy was performed in 1·3 per cent of cases. Caesarean section was performed in 12 cases (4·2 per cent). There were 8 maternal deaths (2·8 per cent).

L. J. Abramowitz

174. **Modern Problems of Diabetic Pregnancy.** (Die diabetische Schwangerschaft und ihre derzeitigen Probleme.)

By G. BAUMGARTEN. *Zbl. Gynäk.*, **83**, 342–346, Mar. 4, 1961. 3 figs. 21 refs.

The author, working in a home for diabetics and in an institute for the study and treatment of diabetes, reports that during the 12 months ending August, 1960, there were 57 diabetic pregnancies, of which 12 occurred in primigravidae. Eleven of these had early vascular lesions, 6 had moderate and 4 advanced ocular changes. He reports that in the Soviet Union such cases are terminated within the first 6 weeks of pregnancy, whereas the attitude in Germany is more conservative. He admits, however, that efficient contraceptive advice would be preferable.

As a rule the diabetic patient was admitted to hospital 6 weeks before term for re-stabilization on insulin and again at 37 weeks of pregnancy for X-ray examination of the foetus and surgical, followed by medical, induction. During labour the patient was switched over to soluble insulin. Oral anti-diabetic drugs were contra-indicated during pregnancy in view of potential risks to the foetus.

The induction-delivery interval ranged from 3 to 72 hours, with an average of 36 hours. 35 per cent of patients were delivered with forceps, Caesarean section was carried out in 6 cases, not because of the diabetes, but mostly for maternal obstetrical indications. There were 5 macerated stillbirths and 3 perinatal deaths which were due to obstetric trauma.

The neonates were starved for 24 hours and fed on human milk from a milk bank.

Bruce Eton

175. **Pregnancy following Ring-Biopsy, Conisation and Amputation of the Cervix.** (Graviditäten nach Ringbiopsien, Konisationen und Portioamputationen.)

By E. BURGHARDT. *Geburtsh. u. Frauenheilk.*, **21**, 225–236, Mar. 1961. 1 fig. 11 tables. 24 refs.

Patients subjected to ring-biopsy, conization and amputation of the cervix for diagnostic purposes in the University Gynaecological Clinic, Graz, were followed up. Two hundred and thirty-two women, under 45 years of age, required no further treatment, and of these 42 (18·1 per cent) conceived after the operation. A total of 57 pregnancies was observed, of which 27 carried to full-term and 10 delivered prematurely (7 are not yet delivered). There were 13 abortions and 1 tubal pregnancy. The premature labours and abortions are analyzed; the authors conclude that the preceding operation could not be regarded as the sole cause. More abortions followed amputation of the cervix, but otherwise no correlation was found between the extent of the operation and the incidence of conception or the outcome of the pregnancy. Labour was prolonged by a third in these women, compared with the average length of labour in the Graz Clinic. The membranes ruptured prematurely in a third of the cases. Cervical dystocia necessitating delivery by Caesarean section occurred in 11·1 per cent of cases.

Peter J. Huntingford

176. **Advanced Abdominal Pregnancy.**

By A. S. BRIGHT and A. H. MASER. *Obstet. and Gynec.*, **17**, 316–324, Mar. 1961. 9 figs. 32 refs.

A case is reported of a secondary abdominal pregnancy at term with a living child in which the placenta was removed at operation. The American literature on abdominal pregnancy for the past 10 years is reviewed, and important points in diagnosis and treatment are brought out.

Vaginal bleeding and abdominal pains occur in almost all cases. Radiological diagnosis can be made from the eccentric position of the foetus, lack of uterine wall outline, clear foetal parts and gas in front of and behind the foetus: foetal parts seen posterior to the lumbar spine in a true lateral view and an empty uterus by hysterogram are pathognomonic.

If diagnosis is not made until the foetus is viable, it is reasonable to wait until the 36th–38th week. The placenta should be left in place and intact if it is attached to vital organs; otherwise, it should be removed if possible. When it cannot be removed at the first operation, a second attempt is advised 9 weeks to 3 years after. If possible, the abdomen should not be drained, otherwise sepsis is likely. If the placenta is not removed, the cord should not be ligated: if it is ligated, the placenta will become cystic.

If laparotomy is not done, infection, suppuration and skeletonization of the foetus may occur, and the abscess may rupture into a viscus. Mummification may take place, when the foetus becomes a greasy green-yellow substance with ultimate calcification.

The infant has a 25 per cent chance of survival and a 10 per cent chance of being normal. Maternal mortality is about 10 per cent.

J. G. Dumoulin

177. **Fertility Rate following Extra-uterine Pregnancy.** (Fertilite nelle donne operate per gravidanza extra-uterina.)

By L. CAGLIERO. *Minerva ginec., Torino*, **13**, 10–14, Jan. 15, 1961. 5 tables. 51 refs.

This paper deals with a follow-up of 181 women out of 248 who were operated on in Turin for ectopic pregnancy over a ten-year period, all having made a complete recovery. The operative procedure was as conservative as possible and in 90 per cent the possibility of a future pregnancy was safeguarded, the remaining 10 per cent having had either a previous contralateral ectopic or some other condition necessitating more radical treatment. On admission, the ectopic pregnancy was the first pregnancy in 23 per cent, 56 per cent had had one or more full-term pregnancies, 12 per cent had only had previous abortions and 3·5 per cent had had a previous ectopic pregnancy.

The follow-up revealed that 51 per cent did not become pregnant again, but some of this was due to voluntary abstention and with the passage of time the figure was likely to be reduced. 37 per cent had one or more full-term pregnancies subsequently, 8 per cent had only abortions and 4·4 per cent had a second ectopic, but of these latter (14 cases) five had had at least one normal full-term pregnancy between the ectopic episodes.

It is therefore concluded that after an operation for extra-uterine pregnancy, although their fertility appears to be reduced and the risk of abortion or of a further ectopic pregnancy remains higher than normal, the occurrence of a normal pregnancy and delivery is by no means rare.

W. C. Spackman

LABOUR

178. **Induction of Labour in Rh-Immunized Patients.** By L. TOWNSEND. *Aust. N.Z. J. Obstet. Gynaec.*, **1**, 27–33, Mar. 1961. 4 tables. 3 figs.

This paper outlines the place of induction of labour in the treatment of 352 Rh-immunized patients during 1957, 1958 and 1959 in the Royal Women's Hospital, Melbourne. Patients who had twin pregnancies, whose pregnancies were terminated, or in whom foetal death occurred before the 28th week were excluded. (During the period there were three twin pregnancies, two of these babies were negative and lived, four were positive and only one survived. Two pregnancies were terminated where the husband was Rh positive and homozygous and there was a past history of two deaths from erythroblastosis. In ten patients foetal death occurred before 28 weeks.)

The other patients were divided into three groups:

Group I consisted of patients in whom antibodies had appeared for the first time or in whom previous children had been only mildly affected. In 1957 these patients had labour induced at 40 weeks. In 1958 and 1959 patients in this group were induced whenever the indirect Coombs titre reached 1 in 64. The hospital staff have now substituted 1 in 256 as a better critical level. When the antibody titre is low or nil at the beginning of pregnancy a rise of two tubes usually means that the baby is Rh positive.

In this Group I the perinatal loss was 10 per cent amongst Rh-positive infants in 1957 and 7 per cent in 1958 and 1959.

Group II contained those patients whose previous infants had required exchange transfusion. In these induction of labour was done at 37 weeks, and in the latter part of the period the colour of the liquor often resulted in a decision to induce before the 37th week. Here the perinatal loss amongst Rh-positive babies was 17 per cent.

Group III consisted of those patients whose previous infant(s) had been lost through erythroblastosis. Here induction was done either at 37 weeks or one week before the time of the previous foetal death whichever was the sooner. The perinatal loss amongst Rh-positive babies was 54 per cent.

Professor Townsend says patients in Group III should have labour induced a week before the previous foetal death had occurred (provided the pregnancy had passed the 33rd week), and the colour of the liquor or the strength of foetal movements would also influence the decision.

Surgical induction of labour using a Drew-Smythe catheter with the use of an intravenous oxytocin drip is an effective method of inducing labour. The method had a 2 per cent failure rate and a perinatal mortality rate due to the induction of less than 2 per cent.

S. Devenish Meares

179. **Transbuccal Pitocin: A New Method for the Induction of Labor.**

By R. D. Rice and R. C. Benson. *Obstet. and Gynec.*, **17**, 297–304, Mar. 1961. 5 tables. 5 figs. 7 refs.

Pitocin trochees of 200 units were placed in 112 patients' mouths (maxillary cheek pouch) to induce labour. Repeated larger doses were given at ½–1 hour intervals until good contractions occurred, as much as 700 units being given in a dose and an accumulated total of 2,700 units being used.

In 85 cases (76 per cent) labour was induced successfully after an average total dose of 2,100 units. There was one neonatal death due to intracranial haemorrhage which was the only serious complication.

J. G. Dumoulin

180. **Induction of Labour by Means of Oxytocin Spray.** (Oxytocin-Spray zur Wehen-Einleitung.)

By K. Baumgarten and W. Hofhansl. *Zbl. Gynäk.*, **83**, 154–158, Jan. 28, 1961. 2 figs. 15 refs.

The authors assessed the possibility of replacing the intravenous drip method of oxytocin induction of labour by the nasal spray. Having confirmed that the synthetic preparation Syntocinon acts on the uterus when administered as a nasal spray, they used it as a modification of the oxytocin sensitivity test. A spray lasting approximately a quarter of a second is applied to each nostril. If a uterine contraction can be felt by the patient and palpated by the examiner within four minutes, the result is regarded as positive. If an identical result is obtained after an interval of 12 to 24 hours the uterus is considered to be suitable for induction of labour.

The spray is applied, contractions are observed and the spray repeated when the strength or frequency of contractions tends to decrease. Two to four applications were frequently sufficient to establish labour, but in some cases treatment had to be repeated during the first and, occasionally, even until the second stage.

The authors found the nasal spray method useful also in cases of primary and secondary inertia, even in the third stage of labour. However, if a uterine response was not obtained within 15 minutes of the nasal application, the patient was regarded as unsuitable for this method.

Tonic uterine contraction was never observed but occasionally a prolonged contraction which lasted up to 4 minutes. [!]

The milk ejecting action of nasal Syntocinon is briefly mentioned.

Bruce Eton

181. **A Clinical and Statistical Review of the Aetiology of Premature Labour.** (Sull'eziologia del parto prematuro. Rilievi clinico-statistici.)

By E. Santi. *Ann. Ostet. Ginec.*, **83**, 257, Mar. 1961. 86 refs.

This is a detailed review of the causes of premature labour, based on 2,229 premature labours occurring in the Obstetrical and Gynaecological Clinic at Milan from 1955 to 1959. During this time there were 23,002 deliveries at term. The incidence of premature labour has been 10 per cent and this has not varied appreciably in different years.

The causes in order of frequency are premature rupture of the membranes (32·8 per cent), toxaemia (8·8 per cent), multiple pregnancy (6·6 per cent) and intrauterine death of the foetus (3·7 per cent).

Less frequent causes include placenta praevia, rhesus incompatibility, tuberculosis, cardiac disease, foetal malformation, renal disease, abruptio placentae, syphilis, hydramnios and uterine malformations.

Slightly over 40 per cent of all premature labours occurred for no apparent cause.

Further studies, especially on the biochemistry of pregnancy, are needed to determine the cause of spontaneous premature labour.

Josephine Barnes

182. **Dysfunctional Labor. I. Prolonged Latent Phase in the Nullipara.**

By E. A. Friedman and M. R. Sachtleben. *Obstet. and Gynec.*, **17**, 135–148, Feb. 1961. 4 tables. 1 fig. 11 refs.

In order to clarify the problems of uterine inertia, the authors have studied its component parts, and this article concerns the initial portion of labour, the latent phase between the onset of regular uterine contractions and the beginning of cervical dilatation.

They show that a long latent phase does not add significantly to the perinatal mortality. Its chief causes include excessive sedation (39 per cent), unripe cervix (18 per cent), false labour (10 per cent) and uterine dysfunction (17 per cent) amongst others. The latent phase can be terminated fairly effectively by oxytocin therapy but artificial rupture of the membranes seems to be a very ineffective method of starting cervical dilatation.

Perhaps the most significant finding was that patients delivered by Caesarean section during the latent phase, for such excuses as inertia, lack of progress, cervical dystocia or exhaustion, were nearly all being operated on unnecessarily, because the majority would have had no trouble once labour was established.

The correct treatment for prolonged latent phase is rest, and later oxytocin if it continues. Whilst some cases will go on to primary or secondary uterine inertia a diagnosis of dysfunctional labour cannot be made whilst the patient is in this phase nor can the outcome of labour be predicted.

J. G. Dumoulin

183. **The Diagnosis and Conservative Treatment of Pelvic Floor Insufficiency.** (Diagnostic et traitement conservateur de l'insuffisance du plancher pelvien).

By K. Semm. *Gynéc. prat.*, **12**, 23–39, 1961. 9 figs. 59 refs.

The author has devised an apparatus by which he can run known volumes of fluid at a known pressure into a thin-walled reservoir inserted into the vagina.

He claims that by relating the distensibility of the vagina to the pressures used it is possible to differentiate three types of pelvic insufficiency:

1. Muscular.
2. Connective tissue.
3. Mixed.

Only the second type will not respond to physiotherapy and must be treated surgically. A chart of suitable exercises for strengthening the muscles of the pelvic floor is included in the article.

Geoffrey Dixon

184. **Hypofibrinogenaemia: Its Relation to Liquor Amnii Embolism.** (L'embolia da liquido amniotico come causa di ipofibrinogenemia ostetrica.)

By D. GIACOPINO, L. RUOZZI and D. COLAVITA. *Minerva ginec., Torino*, **12**, 982–986, Oct. 31, 1960. 5 figs. 20 refs.

It is widely held that under certain circumstances, especially during the first stage of labour in cases of hydramnios, multiple pregnancy and where first stage contractions are strong, liquor amnii can enter the maternal circulation through the open mouths of lower segment veins and that this can cause serious defect in the powers of the blood to clot by destroying maternal fibrinogen.

The authors injected increasing amounts of human liquor amnii into the blood stream of guinea-pigs and calculated the coagulability of their blood at intervals thereafter. They found that it was only when the liquor injected reached a proportion of 1 in 17 of the total circulating blood that a serious loss of coagulability was evidence, and even so it took eight hours for maximum effect. If, however, the proportion was increased to 1 in 13 the effect was rapid and severe and the anima quickly died. It would appear from this that small amounts of liquor amnii escaping into the maternal circulation are of little clinical importance, and that in the absence of other established factors it requires a large and rapid invasion of the maternal blood stream by liquor amnii to produce a really serious defect of coagulability.

W. C. Spackman

185. **The Diagnosis of the Position of the Foetal Skull.**

By L. W. COX. *Aust. N.Z. J. Obstet. Gynaec.*, **1**, 40–45, Mar. 1961. 6 figs. 2 refs.

For 12 years Professor Cox of the University of Adelaide has been using the occipital bone as a landmark of the foetal skull. Every obstetrician has at some time made a wrong diagnosis of the position of the foetal skull using the classical landmarks. This is due to the imperfection of the traditional landmarks as regards their permanent and constant recognition. Greater reliance should be placed on the external occipital protuberance and the "nodular" feel of the two superior curved lines of the occipital bone, which on palpation in obstructed labour feel almost like tubercles.

In the foetal skull the hinged joint of Budin (1876) between the anterior end of the tabular part and the two exoccipitals is cartilaginous and is not ossified at birth. As a result considerable bending of the occipital bone can take place with moulding. This leads to the external occipital protuberance becoming more prominent and the superior curved lines appearing like bony "nodules". This area seems to be remote from the area likely to be covered by caput. Cox has never found it obscured.

This moulding and prominence rapidly disappear shortly after birth. The obstetrician can rely on the occipital bone almost exclusively for his diagnosis of the position of the foetal skull. It is not necessary to feel for an ear after pushing the head up. The palpation of the occipital bone is useful in checking the application of the forceps blades before extracting the foetal head. A tutor can readily check this when a pupil has applied the forceps.

The only possible confusion that may arise is to mistake the frontal bone for the occipital. This mistake will occur only with carelessness. If the frontal bone has a boss this might be mistaken for the external occipital protuberance but the characteristic prominence of protuberance plus "nodules" is missing.

S. Devenish Meares

186. **Compound Presentations.**

By W. J. SWEENEY and R. C. KNAPP. *Obstet. and Gynec.*, **17**, 333–341, Mar. 1961. 10 tables. 11 refs.

As used here the term compound presentation includes vertex presentation with prolapse of one or more limbs, and breech presentation with prolapsed arm or arms. In the authors' series of 74 cases it occurred once in 1,300 deliveries. The three main factors associated were twinning, prematurity and a high presenting part. The predominant type of presentation was vertex-arm. Prolapse of the cord occurred in 10 cases.

The prolapsed extremity was replaced in 10 cases; there were 26 versions with extraction, 14 Caesarean sections and 24 cases in which no special treatment was given. The perinatal mortality was 25 per cent, and 7 (9·4 per cent) of the deaths were attributed to mismanagement. There were 2 maternal deaths.

It is probably best not to manipulate the prolapsed extremity, keeping Caesarean section for cases with such difficulties as prolapsed cord. Version and extraction, except in some instances of second twins, has no place in management of compound presentation.

J. G. Dumoulin

187. **A Case of Ruptured Uterus and Cardiac Arrest, with Recovery.**

By G. H. HARRIS, M. K. THOMPSON and V. P. WORDSWORTH. *Brit. med. J.*, **1**, 715–717, Mar. 11, 1961. 3 refs.

The patient, a married woman aged 27, had been delivered normally of a living infant weighing 6 pounds 6 ounces in 1954. Two years later uncomplicated curettage had been performed and in 1957 she had had a spontaneous abortion.

During the pregnancy in question, an unsuccessful attempt at version was made at the 32nd week and a week later spontaneous version had occurred. Labour commenced soon after rupture of the membranes following a medical induction (oil, bath and enema) and rupture of the posterior wall of the uterus occurred when the cervix was three-quarters dilated.

A blood transfusion was set up and anaesthesia induced (300 mg. thiopentone, 50 mg. scoline, 75 mg. pethidine with nitrous oxide/oxygen/cyclopropane).

Total hysterectomy was performed and cardiac arrest occurred during closure of the pelvic peritoneum. This was thought to have been precipitated by head down tilting and the injection of a small dose of thiopentone. Cardiac massage was performed and the heart started beating again in 3 minutes. Post-operative measures, including induction of hypothermia were largely those laid down by Maciver *et al.* (*Lancet*, 1958, **2**, 544) for the treatment of severe head injuries.

The patient remained in coma for one week and presented a picture of tonic fits superimposed on a decerebrate posture with initial pyrexia. When she left hospital after a stormy convalescence there was still evidence of brain damage but one year later she is described as being "a reasonable member of society". She still had some cerebellar dysfunction and there had been a change (for the good) in her temperament. *R. W. Grayburn*

OBSTETRIC OPERATIONS

188. **Experiences with the Malmström Vacuum Extractor.** (Sul' impiego del vacuum-extractor di Malström.)

By A. BARICALLA. *Minerva ginec., Torino*, **12**, 1110–1115, Nov. 30, 1960. 1 table. 2 figs. 12 refs.

A description of this now well-known instrument and of its use, including cautions about its limitations, is followed by details of 46 cases in which it was employed. The cups are of three sizes, 3, 4 and 5 cm. in diameter to accord with the degree of dilatation of the cervix encountered. The effective negative pressure (about 0·6 to 0·8 kg. per square cm.) is to be reached only by gradual steps over a period of 10 to 15 minutes. The cups can usually be applied to the presenting part without anaesthesia and the knob on the cup should be directed towards the occiput so that in the course of the extraction it can, if desired, be pressed anteriorly to assist forward rotation. Traction can be continuous by weight and pulley (as was used with the Willett's scalp forceps), but in all second stage cases maximum traction should coincide with uterine contractions and must not approach the force often used for difficult forceps deliveries.

In the cases recorded, the most usual indication was delay in the second stage. Other indications also were similar to those for forceps delivery. In four cases it was successfully applied to the extended breech.

[The author expresses himself as well satisfied with its usefulness but the abstracter would suggest that most obstetricians accustomed to the use of forceps would find little use for it (although conceding that it can be applied without anaesthesia) except in those tiresome cases of prolonged delay in obtaining full dilatation of the cervix with the membranes ruptured.]

W. C. Spackman

189. **An Electric Pump for Vacuum-Extraction.** (Technische Hilfen für die Vakuumextraktion.)

By E. RÜTHER and K. SOKOL. *Geburtsh. u. Frauenheilk.*, **21**, 245–248, Mar. 1961. 2 figs. 9 refs.

The authors have devised an electric pump that will induce and maintain the vacuum necessary for the application of the Malmström vacuum extractor. The desired negative pressure can be selected by means of push-buttons. A maximum negative pressure of 1 kg. per sq. cm., which is developed in 4 stages, can be obtained with the pump. Two machines have been designed: a small portable one; and a larger machine with a built-in secretion and vacuum bottle, and also a selector that enables the rate of development of the vacuum to be controlled. *Peter J. Huntingford*

190. **The Foetal Mortality and Morbidity Following Delivery with Forceps and Vacuum Extractor.** (Die kindliche Mortalität und Morbidität bei Zangen- und Vakuumextraktionen.)

By J. HOLTORFF. *Zbl. Gynäk.*, **83**, 261–268, Feb. 18, 1961. 1 fig. 7 tables. 15 refs.

The incidence of delivery with the vacuum extractor (VE) at the Dresden Medical School rose from 1·9 per cent in 1959 to 4·6 per cent in 1960. At the same time, the number of forceps deliveries decreased. The author considers that foetal asphyxia has become the main indication for forceps delivery, as it permits a more rapid and certain delivery. The VE has become the instrument of choice in cases of inertia, failure of progress, intrapartum pyrexia and maternal diseases complicating pregnancy. There is, however, a place for the VE in the treatment of imminent asphyxia, if the head is high, a type of case in which forceps delivery is attended by great hazards to the child.

There were 2 foetal deaths amongst 119 infants delivered with the VE, an incidence of 1·7 per cent. One of these had intra-cranial haemorrhages and the VE had been applied on account of foetal distress.

By contrast, the gross foetal mortality following forceps delivery during the years 1958 to 1960 was 12·6 per cent (16 out of 127). The corrected mortality was 6·3 per cent.

The author is convinced that the usefulness of the VE has been established beyond doubt, but he points out that obstetricians, before becoming proficient in the use of the instrument will experience some disappointments, such as infants with infected cephalhaematoma, facial paresis, infection of the scalp, feeding difficulties, restlessness and perhaps cerebral irritation, particularly if both VE and forceps are used for the same child. *Bruce Eton*

191. **Spontaneous Deliveries after Caesarean Section.** (Spontangeburten nach Kaiserschnitt.)

By R. GANSE. *Zbl. Gynäk.*, **83**, 537–540, Apr. 8, 1961. 10 refs.

In spite of a high incidence of spontaneous deliveries after Caesarean section at the Dresden Medical School during the period 1948–1958, there has not been any case of ruptured uterus, acute or "silent". Comparison of two successive five-year periods showed an increasing trend in the incidence of vaginal delivery after Caesarean

section from 63·3 to 71·4 per cent amongst those patients who had a further pregnancy and were traced.

The absence of any case of rupture of the uterus is partly attributed to the almost exclusive use of the transverse lower segment incision, partly to the method of suturing in layers, using interrupted stitches, completed by two layers of peritoneum over the lower segment, and also partly to the routine precaution of digital examination of the interior of the uterus after each vaginal delivery in these cases.

Bruce Eton

LACTATION

192. **Intranasal Use of Synthetic Oxytocin in the Management of Breast Feeding.**

By P. J. HUNTINGFORD. *Brit. med. J.*, **1**, 709–711, Mar. 11, 1961. 26 refs.

A group of 24 patients to whom oxytocin ("syntocinon") was administered by means of a nasal spray was compared with another group of 24 patients who received a placebo only.

It was found that breast feeding was more easily established in the first group and there was also an improvement of milk production. The use of oxytocin insured more complete, more rapid and easier emptying of the breast by the baby. Oxytocin may exert a galactopoietic as well as a galactokinetic effect.

Slight bleeding from the nose occurred in one case but no serious side effects were noted.

No significant reduction in the incidence of early breast engorgement was obtained but this may be due to the fact that most of the patients had finished their sprays by the fifth day.

R. W. Grayburn

INFANT

193. **Place of Maternal Rubella in the Aetiology of Congenital Heart Disease.**

By M. CAMPBELL. *Brit. med. J.*, **1**, 691–696, Mar. 11, 1961. 30 refs.

The risk of abortion and of congenital malformation in the child following maternal rubella is said to be between 30 and 70 per cent during the first few weeks of pregnancy, between 25 and 55 per cent in the second few weeks, between 20 and 40 per cent during the third few weeks and between 10 and 25 per cent during the fourth few weeks; later than this there is no increased risk. Deafness is the greatest risk, then congenital heart disease and then cataract, mental defect and microcephaly.

Maternal rubella in pregnancy is probably responsible for between 2 and 4 per cent of all cases of congenital heart disease. The most common congenital heart lesion is persistent ductus (58 per cent); then comes ventricular septal defect (18 per cent) and the two are combined in about 6 per cent of cases. Atrial septal defect, pulmonary valvular stenosis and Fallot's tetralogy each occur in about 6 per cent of cases.

Other viral infections, such as mumps, measles, epidemic hepatitis and poliomyelitis can produce similar malformations occasionally.

R. W. Grayburn

194. **The Mode of Action of Analeptic Drugs in the Newborn.** (Neue Untersuchungsergebnisse über die Wirkung atmungsanregender Medikamente auf das Neugeborene).

By E. SALING. *Geburtsh. u. Frauenheilk.*, **21**, 237–245, Mar. 1961. 1 fig. 5 tables. 4 refs.

Blood samples were withdrawn from the umbilical arteries of 70 normal infants by means of a catheter inserted immediately after birth, before and after the intravenous injection of the following analeptic drugs: lobeline, coramine, and Micoren (a mixture of n-crotonyl-α-ethylaminobutyric and n-crotonyl-α-propylaminobutyric dimethylamides). The oxygen-saturation of the arterial blood of 48 infants fell after the injection of these drugs, in spite of the fact that respiratory excursions were increased. Samples of blood were also obtained from the arch of the aorta (above the opening of the ductus arteriosus); oxygen-saturation fell in 10 of 14 normal infants after an intravenous injection of Micoren, in 6 of 9 after lobeline, and in 4 of 6 after coramine. By inserting two catheters, the arterial tension was measured in the pulmonary artery and in the arch of the aorta; by injecting dye into the pulmonary artery, the volume of blood flowing through the lungs per minute, and the cardiac output, were measured before and after the administration of an analeptic drug. The drugs caused an increase in pulmonary blood flow and a rise in pulmonary artery pressure. Similar results were obtained in asphyxiated infants; if anything, the fall in oxygen-saturation was even more marked than in the normal infants.

The author concludes that the beneficial effect of the increased respiratory excursion produced by analeptic drugs is offset by their action in causing pulmonary vasoconstriction, which in turn leads to pulmonary hypertension and a rise in the rate of blood flow through the lungs. The increased rate of blood flow through partially atelectatic lungs does not allow sufficient time for its adequate oxygenation.

[This is a particularly thorough study of the basic physiological changes occurring in the infant immediately after birth. It also provides evidence to back up the widely held clinical impression that analeptic drugs are of very little use in resuscitation of the newborn.]

Peter J. Huntingford

GYNAECOLOGY

DISORDERS OF FUNCTION

195. **Clinical Value of Oestrogen Assay in Gynaecology and Obstetrics.** (Klinische Bedeutung der Östrogenbestimmung in der Gynäkologie und Geburtshilfe.)

By H. IGEL, K.-H. BERGMANN and G. ITTRICH. *Zbl. Gynäk.*, **83**, 518–524, April 1, 1961. 11 figs. 6 refs.

Using the method previously described by Ittrich, serial oestrogen assays showed one peak at the time of ovulation and another half-way through the luteal phase

of the menstrual cycle, indicating the time of maximal functional activity of the corpus luteum. In 53 pregnancies the urinary total oestrogen excretion rose steadily from 3·0 mg. per diem during the third month, to 38·5 mg. during the tenth lunar month. With parturition a steep drop in oestrogen excretion occurred. Two hours after delivery there was a fresh rise followed by an abrupt fall. A second rise took place 18 hours post partum.

[If subnormal excretion values are found over a prolonged period of time a disturbance of placental function should be suspected. They are a certain criterion of missed abortion or intra-uterine death, even when biological tests of pregnancy are still positive.] *Bruce Eton*

196. **The Syndrome of Pelvic Pain in Women.**

By H. C. TAYLOR, JNR. *Aust. N.Z. J. Obstet. Gynec.*, **1**, 5–16, Mar. 1961. 12 tables. 29 refs.

Professor Taylor of Columbia University, New York, has published five previous papers on this subject during the last 25 years. By the pelvic pain syndrome is meant pelvic pain in the absence of any detectable pathology.

Although it is common its causes and nature are little understood. It is most often found in the years of greatest reproductive and sexual activity in married women with small families, and it is associated with a high incidence of abortion. The site of the pain may be suprapubic, low in the back, rectal or coccygeal, and there may be associated dysmenorrhoea and dyspareunia. Many other pelvic and general symptoms may also be present, and it is noteworthy that in one-third of the patients breast symptoms are also present. Psychoneurotic symptoms are often obvious.

On examination anatomical lesions are absent, though the differential diagnosis from such conditions as endometriosis and chronic pelvic inflammatory disease is often hard to make. There is low abdominal tenderness, mostly deep but sometimes superficial. On bimanual examination the utero-sacral ligaments are tender and there is pain on moving the uterus.

The nomenclature and previous concepts of the syndrome are reviewed. It has been attributed to inflammation, smooth muscle spasm, chronic pelvic congestion or a general autonomic disorder. The author believes that the syndrome is due to an abnormal condition of the pelvic vascular system with hyperaemia and venous stasis probably resulting primarily from a psychosomatic disorder. Organic alteration of the tissues subjected for years to the adverse environment of an unfavourable circulation may eventually appear. The pelvic circulation can be affected by anatomical, positional, hormonal, inflammatory or psychological factors.

The evidence that venous stasis or tissue oedema is present in these patients is supported by the pre-menstrual timing of the symptoms, the associated breast engorgement, the enlargement of the cervix and uterus, occasionally by microscopic examination of the tissues, by X-ray studies after injection of radio-opaque material into the pelvic veins, and by thermal conduction studies of pelvic blood flow.

In his own investigations and in the literature the author has found much evidence of a psychiatric factor and support for the idea that such factors can alter the vascularity of the pelvic organs.

In treatment, though it is not often necessary to seek consultation with a psychiatrist, the gynaecologist may enquire into sources of tension, family or financial worries and problems of marital relationship. Conservative treatment consists of rest, both physical and sexual, the correction of descent of the uterus by a pessary, local treatment of the cervix, and hormone therapy. In rare cases in patients approaching the menopause suppression of ovarian function by X-rays may prove very effective. Such operations as uterine suspension, partial or unilateral oöphorectomy and section of the utero-sacral ligaments have a very limited place.

In patients over 35 years of age, who have completed their families, and in whom many months or years of conservative therapy have failed, and who have consulted a psychiatrist without relief, hysterectomy can be counted upon to give a considerable measure of relief of local symptoms. *S. Devenish Meares*

197. **Serum Lipid Patterns Before and After Castration of the Human Female.**

By R. W. STANDER and J. K. LEIN. *Surg. Gynec. Obstet.*, **112**, 450–454, Apr. 1961. 1 table. 14 refs.

Clinical observations and experimental work suggest an association between abnormal serum lipid patterns and the development of atherosclerosis. There is evidence that ovarian secretion provides protection against coronary artery disease and that ovarian ablation may lead to changes in the serum lipid pattern. The rarity of coronary artery disease in women under 40 years and the increased incidence after the menopause suggest a relation between ovarian function and the inhibition of atherosclerosis.

The authors studied the total serum cholesterol and phospholipid levels in 24 healthy women of reproductive age and 28 gynaecological patients, 23 of whom underwent surgical, and radiation, castration.

The results suggest that factors other than the presence of ovarian tissue influence the partition of serum lipids but that the over-all effect of the removal of ovarian tissue was an elevation of total cholesterol and phospholipid.

Clarification of the role of ovarian function in homeostasis of serum lipids and the relation to coronary artery disease may result from research; in the meantime the authors suggest that as the gonadal tissue may still play a vital part in metabolism, conservatism should be advocated unless oöphorectomy is definitely indicated for primary disease. *A. E. R. Buckle*

198. **Endocrine Causes of Intersex.** (Die endokrinen Beziehungen der Intersexualität.)

By A. JAKOBOVITS. *Zbl. Gynäk.*, **83**, 573–588, Apr. 15, 1961. 4 figs. 135 refs.

Three chromosomal types of intersex occur equally in men and women: true hermaphroditism, Klinefelter's

and Turner's syndromes. In a systematic review of endogenous and exogenous causes of intersex the author discusses those arising in the male gonads: testicular feminisation, interstitial cell tumours, Sertoli cell tumours, and granulosa cell tumours; in the female: hyperthecosis (Stein-Leventhal syndrome) arrhenoblastoma, hilus cell tumours, luteoma and masculinovoblastoma. Adrenocortical causes include feminizing tumours in the male, and hyperplasia (adrenogenital syndrome) and virilizing tumours in the female.

Exogenous causes of intersex are: oestrogen medication in the male; in the female, treatment with androgens and the recently observed effects of potent progestogens on the female foetus. Jakobovits also points out that occasionally androgens derived from a male foetus may have slight virilizing effects on the mother during pregnancy.

Bruce Eton

199. **Primary Endometrial Aplasia.**

By F. BENJAMIN. *S. Afr. med. J.*, **35**, 81–82, Feb. 4, 1961. 15 refs.

Three cases of congenital absence of the endometrium without associated endocrine dysfunction or uterine hypoplasia are described. Exploration of the literature failed to reveal any reports of primary amenorrhoea due to congenital absence of the endometrium.

In one case, a patient of 45 years, hysterectomy was performed for multiple fibromyomata. She had never menstruated. Several sections of the uterus failed to reveal endometrium.

In all three cases laparotomy was performed and the findings were confirmed by biopsy of the lining of the uterine cavity.

L. J. Abramowitz

INFECTIONS OF THE REPRODUCTIVE ORGANS

200. **Genital Tuberculosis Associated with Other Pelvic Pathology.** (Sulla patologia genitale associata alla tbc. genitale femminile.)

By C. DURANDO and F. VISCHI. *Minerva ginec., Torino*, **12**, 889–908, Oct. 15, 1960. 11 figs. 4 tables, 58 refs.

Tuberculosis in the female pelvic organs is not uncommonly associated with other pathological conditions which often give rise to difficulties in differential diagnosis as well as unfortunate results in treatment. If this association is not recognized, dormant foci of tuberculosis can be reactivated, sometimes with alarming results, especially if treatment involves disturbing anatomical planes and opening up cellular communicating channels. Moreover the very association of a second infection with a tuberculous lesion reacts unfavourably on both. A silent or quietly active tuberculous salpingitis or endometritis associated with a septic cervical erosion treated by cautery or conization can lead to a flare-up of the more serious disease, as can an injudicious hysterosalpingography. This association of tuberculosis with other septic conditions was found in 30 per cent of the 500 cases reviewed by the author. Tuberculosis is somewhat rare in association with fibroids but is less uncommon with endometriosis and can lead to much difficulty in diagnosis in the latter. Another point to note is that pelvic tuberculosis, even though long since healed, can be an aetiological factor in ectopic pregnancies. As for the rare association of tuberculosis with malignant disease, this is regarded as casual, with the possible exception of vaginal or vulval carcinomas where a long-continued discharge has irritated these tracts.

When tuberculosis is recognized, it must be carefully and thoroughly treated before treatment of other conditions is contemplated.

W. C. Spackman

201. **Investigation of the Clinical Significance of *Haemophilus vaginalis*.** (Untersuchungen über die klinische Bedeutung von "Haemophilus vaginalis".)

By J. KÜMMEL and W. RITZERFELD. *Geburtsh. u. Frauenheilk.*, **21**, 249–258, Mar. 1961. 1 fig. 6 tables. 14 refs.

The authors investigated 800 patients complaining of excessive vaginal discharge. *Haemophilus vaginalis*, a Gram-negative pleomorphic cocco-bacillus, was isolated in 171 women (21·4 per cent), and in a further 89 women (11·1 per cent) this organism was thought to be responsible for the observed vaginitis. *H. vaginalis* is regarded as a vaginal pathogen, which causes vaginitis characterized by a thin, grey, homogenous and inoffensive discharge. The organism was always sensitive to tetracyclines; patients responded to treatment either with vaginal pessaries, 100 mg. on alternate days for 10 days, or to oral therapy, 250 mg. q.d.s. for 4–6 days. Coincident treatment of the husband is recommended as the male was found to be a carrier of the organism in a number of cases.

Peter J. Huntingford

202. **The Treatment of Pelvic Inflammation with Glucocorticoids.** (Behandlung entzündlicher Adnexerkrankungen mit Glucocorticoiden.)

By H. TASCH. *Geburtsh. u. Frauenheilk.*, **21**, 354–359. Apr. 1961. 1 table. 4 refs.

Sixteen patients with acute salpingitis and 90 with subacute or chronic salpingitis who had tubal or tubo-ovarian masses were treated with a combination of prednisolone, penicillin (300,000 units daily) and streptomycin (1 g. daily). Prednisolone was given in decreasing doses over 14 days; the first 50 patients were started on 15 mg. daily; in the second group therapy was begun intravenously, starting with 50 mg. on the first day of treatment, oral therapy was resumed after the fifth day. In the 16 acute cases none of the women developed adnexal swellings, and 4 have since become pregnant. The adnexal swellings present in 59 (65·5 per cent) of the 90 sub-acute and chronic cases resolved completely, and 4 of these patients have since become pregnant. In a further 25 patients there was considerable improvement. In only 7 patients was there no improvement at all; and all but 2 felt much better. It was necessary to stop treatment in one patient who had an ulcer. The author considers that the combination of antibiotic and steroid therapy represents an advance in the treatment of pelvic inflammation in the female.

Peter J. Huntingford

NEW GROWTHS OF THE REPRODUCTIVE ORGANS

203. The So-called Perinuclear Halo.

By E. D. GIROLAMI. *Obstet. and Gynec.*, **17**, 175–182, Feb. 1961. 11 figs. 19 refs.

The term perinuclear halo is used to define a morphological change usually present in the squamous cells of the uterine cervix during certain types of inflammation. Using special stains, the author shows that the clear area is not around the nucleus but is intranuclear. In fact, the "nucleus" is the chromosome frame, the "halo" is the nucleoplasm, and the membrane is the nuclear membrane.

J. G. Dumoulin

204. Office Examination of Fresh Cancer Cells by Interference Phase Microscopy.

By D. V. HIRST. *Amer. J. Obstet. Gynec.*, **81**, 138–139, Jan. 1961. 8 figs. 1 ref.

The study of fresh or living unfixed cells by means of conventional microscopes has been discouraging because the fine detail in the cells appears transparent in visible light, while fixing and staining induces changes in the cells before evaluation, so that our knowledge of histology and pathology is based on artefacts. The author finds the Baker interference microscope manufactured by the American Optical Company ideal for examination of fresh material.

The present report concerns cytological spreads obtained from the uterine cervix and mounted either in normal saline or in 5 per cent dextrose, lactated Ringer's solution, and covered with a glass slip. All the material was fresh, unfixed and unstained. All cancer cells so far observed have lobulated outline, some with finger-like prolongations, and have fine granules in the cytoplasm; the nuclei are large and swollen and the cells are extremely fragile and lyse easily, so that globules of cytoplasm float free in the mounting fluid. These are significant differences from anything so far seen in fixed and stained specimens. One can only ask with the author:

(1) Whether this is "the true face of cancer";
(2) Whether the spontaneous lysing of the cells is a virus effect; and
(3) Whether the dissemination of cytoplasm, either by separation of lobules or by spontaneous lysis, is a mode of spread of the disease.

F. J. Browne

205. Histochemical Observations on Leucinaminopeptidase-Activity (LAP) in Cases of Carcinoma of the Cervix. (Histochemische Beobachtungen über Leucinaminopeptidase-Aktivität bei Kollumkarzinomen.)

By K. FUHRMANN. *Zbl. Gynäk.*, **83**, 213–219, Feb. 11, 1961. 5 figs. 45 refs.

As studies of ferments carried out on tumour homogenates do not take into account differences between parenchyma and stroma, nor between central and peripheral portions of tumours, the authors thought it would be interesting to study the distribution of ferments with histochemical methods for demonstrating aminopeptidases. The material was provided by 100 cases of carcinoma of the cervix, in which the behaviour of the LAP was assessed with the azo-dye method.

The most striking observation was the absence or scarcity of LAP activity within the tumour cells and by contrast a much higher activity in tumour stroma. Massive tumours show clearly the absence of LAP in the centre and perhaps scanty activity at the periphery. Cancers which grow as finger-like processes in narrow strands more often may reveal some LAP activity within the tumour cells, but again mainly at the marginal portions. Larger tumour areas with peripheral stroma show increased enzymatic activity in the stroma. Such an increase is also found in granulation tissue.

These observations are thought to indicate that the LAP activity in the stroma of a cancer is a normal property of connective tissue cells undergoing proliferation and is not related to the invasiveness of the tumour.

Bruce Eton

206. Carcinoma of the Cervix.

By M. TERRIS and M. C. OALMANN. *J. Amer. med. Ass.*, **174**, 1847-1851, Dec. 3, 1960. 18 refs.

The authors present an epidemiological report upon the case histories of 122 patients (59 white and 63 negro) admitted to the Charity Hospital, New Orleans, with histologically confirmed squamous cell carcinoma of the cervix. An identical number of cases with other gynaecological conditions were subjected to the same interrogation and used as controls. Questions covered a wide field including age, race, pregnancies, use of contraceptives, marital history, sexual relationships, douching practices, education and circumcision of the husband. The data obtained in both groups are arranged in 12 tables.

No association was found between carcinoma of the cervix and the number of pregnancies. Some rather uncertain association was found with syphilis and with non-circumcision of the husband. Significant association was found between carcinoma of the cervix and early marriage, extramarital relations, multiple marriages, early coitus, frequent coitus and non-use of contraceptives. The hypothesis that coitus is a major factor in the genesis of carcinoma of the cervix is supported by this study, but the mechanism involved is uncertain. The most likely explanation is frequent contact of the cervix with a carcinogenic agent over many years. Significantly fewer patients than controls used contraceptives and the possibility of some component of smegma as the carcinogenic agent requires further investigation.

[The suggestion that contraceptive barriers may prevent carcinoma of the cervix is not new but merits further consideration in view of the recent introduction of oral contraceptives.]

D. W. James

207. The Relationship of Sexual Activity to Cervical Cancer.

By A. J. PEREYRA. *Obstet. and Gynec.*, **17**, 154–159, Feb. 1961. 1 table. 21 refs.

A survey for cancer of the cervix in prisoners of the California Institution for Women in 1957–58 showed the disease to be 6 times more prevalent in this group than in comparable non-prison groups. This disparity applied to cancer of the cervix only and not other forms of cancer. Pelvic infection was commonly found in the group but the dominant characteristic of the group seemed to be promiscuous sexual activity. *J. G. Dumoulin*

208. **Cervical Carcinoma: Growth and Spread and Some Adjunctive Therapeutic Measures.**

By A. W. Diddle, K. A. O'Connor and H. H. Jenkins. *Amer. J. Obstet. Gynec.*, **81**, 166–173, Jan. 1961. 36 refs.

This is a study of 505 patients with invasive cancer of the cervix, treated between 1949 and 1959. It was learnt that ill-nourished, edentulous and anaemic women, often with hypoproteinaemia and avitaminosis, are less likely to tolerate a therapeutic dose of irradiation. Adequate intake of food may make the difference between a patient's being able and not being able to complete treatment. Some ill-nourished women irradiated without the benefit of supportive measures were believed to have died as a direct result of irradiation, 3 from severe enteritis, one from perforation of small bowel, and 2 from sloughing voluntary muscles. Anaemic patients often required as long as 6 months to recuperate after treatment. The woman who is to be irradiated is therefore instructed to have a high protein, high vitamin and high calorie diet.

Prophylactic antibiotics are not advised, except that 1·2 million units of penicillin G. are given intramuscularly at the time of intracavitary insertion of radium. Since this was started, only 1 of 250 women receiving intracavitary radium had a temperature elevation to 101° F. or over. The authors use radical hysterectomy and pelvic lymphadenectomy without oöphorectomy in young women with lesions graded as Schmitz stage 1 or 2 because removal of ovaries in young women predisposes to osteoporosis at an early age, and because of the mental problems of castration to the patient. The ovaries are rarely involved in cervical cancer, and there is no evidence that their retention enhances the growth of residual cancer. *F. J. Browne*

209. **Carcinoma-in-situ, Early Invasive Carcinoma and Clinical Cancer of the Cervix.** (Carcinoma in situ, beginnendes Karzinom und klinischer Krebs der Cervix uteri.)

By K.-G. Ober, C. Kaufman and H. Hamperl. *Geburtsh. u. Frauenheilk.*, **21**, 259–297. Mar. 1961. 9 figs. 10 tables. 86 refs.

Four hundred and fifty-four cases of carcinoma of the cervix were divided into 4 groups. For this purpose attention was paid to the method of diagnosis of the individual cases, rather than to the "staging", which depends on the extent of the growth.

1. Clinical cancer (301 cases). The nature of the lesion was obvious on simple clinical examination; histological study only served to confirm the diagnosis.

2. Histologically diagnosed cancer (35 cases), in which histological study was essential for the diagnosis.

3. "Early cases" (108 cases) were those that required special diagnostic techniques for their discovery, e.g., cytology, colposcopy, colpo-microscopy, and conization. They include all the variations of carcinoma *in situ* and the earliest stages of invasive carcinoma.

4. Unclassified lesions (10 cases).

The authors argue that if the associated risks of treatment are weighed against the likelihood of a recurrence, radical treatment is essential for clinically or histologically diagnosed cases of cancer (macrocarcinomata), whereas this is less certain for the "early cases". The border-line between those lesions which should be treated as energetically as possible and those in which less dangerous forms of treatment would suffice, lies somewhere within the group of cases usually classified as stage 1.

Staging of carcinoma of the cervix, as used at present, does not offer the best guide to the treatment required. Stages 1 and 2 include cases of clinical cancer, but also a variable number of "early cases", the number of which varies from hospital to hospital according to the diagnostic techniques in use and the evaluation of the histological findings. Therefore, it is possible for the absolute cure rates of different hospitals to differ by as much as 10 per cent, in spite of comparable clinical material, without the better results necessarily meaning that the treatment was more efficacious. In order to obtain a reliable assessment of the value of various treatments for carcinoma of the cervix, comparisons should be confined to clinical cancer.

[This is a long and detailed article containing a complicated argument, which attempts to answer the question: "why do the absolute cure rates for carcinoma of the cervix reported by different hospitals differ so widely?" The authors succeed in making their point, namely a plea for a more critical and practical classification of cases so that true comparisons can be made. The paper also contains a valuable review of the literature and a list of references related to the diagnosis and treatment of pre-invasive and early malignant lesions of the cervix.] *Peter J. Huntingford*

210. **Colposcopic Findings and Localization of Carcinoma In Situ.** (Kolposkopischer Befund und Lokalization des Carcinoma in situ).

By G. Kern and H.-P. Bötzelen. *Arch. Gynäk.*, **194**, 564–585, 1961. 7 tables. 30 refs.

The histological patterns of 105 carcinomata-in-situ were compared with the pre-operative colposcopic findings. In 60 cases malignancy was suspected on colposcopy, and 45 cases did not give rise to any apprehension on colposcopic examination. The colposcopically suspicious areas were situated in the vicinity of the histological changes but the histological changes were often more or less extensive than was anticipated by colposcopic examination. In only 16 of the 60 colposcopically positive cases was there close correlation between the histological and colposcopical findings.

In the remaining 44 cases the histological lesion was found to be in the vicinity of the colposcopically suspect area but not in the exact location. Even among these cases areas which appeared normal on colposcopic examination were subsequently shown to harbour carcinomatous tissue on histologic section; e.g., in 11 cases histologically malignant changes were found to be present in anterior and posterior lips of the cervix whereas only one lip appeared to be abnormal on colposcopic examination.

Forty-five cases of carcinoma-in-situ did not arouse any suspicion of malignancy on colposcopic investigation. Of these 34 lesions were situated on the surface and 11 in the intracervical canal. It appeared therefore that the localization of the disease in the intracervical canal, i.e., outside the range of the colposcope, was not the only cause of false negative colposcopy findings. The authors conclude that negative colposcopy findings by no means guarantee absence of cervical cancer.

E. Wachtel

211. **The Examination of Lymph Nodes Removed During the Wertheim-Meigs Operation.** (Lymphknotenbefunde nach Wertheim-Meigscher Operation.)

By C. A. AHRENS and S. TSCHOKE. *Geburtsh. u. Frauenheilk.*, **21**, 219–224, Mar. 1961. 2 tables. 43 refs.

The lymph nodes removed from 85 patients with carcinoma of the cervix treated by the Wertheim-Meigs operation without preliminary irradiation in the Gynaecological Clinic, Hamburg, Altona, were reassessed by serial section. The number of glands involved were analyzed according to the stage of the growth, and then compared to the findings obtained by routine histological examination of the surgical specimen. Serial sections showed that the lymph nodes were involved in 25 per cent of stage 1 cases compared with 11·5 per cent involvement that was found on routine histological examination; the comparable figures for stage 2 growths were 41 per cent and 36 per cent respectively.

Peter J. Huntingford

212. **The Combined Treatment of Carcinoma of the Cervix with Full Irradiation Therapy Followed by Radical Pelvic Operation. Second Progress Report on a Series Now Numbering 95 Cases.**

By C. S. STEVENSON. *Amer. J. Obstet. Gynec.*, **81**, 156–165, Jan. 1961. 4 tables. 3 refs.

This is a survey of 95 cases of cancer of the cervix, stages 1 and 2 and early stage 3, treated between January, 1949, and September, 1959. The operative treatment following irradiation consisted in a radical Wertheim transabdominal excision of the upper genital tract, the broad ligaments and the pelvic lymph nodes, and was followed by careful study of all excised tissues for residual carcinoma. In the last 40 cases the ureter has not been dissected from its bed in the base of the broad ligament. Each patient was prepared for operation during a 4 to 10 day period of hospitalization during which anaemia was corrected, and the patient was encouraged to eat a high protein diet, and given multi-vitamins and 600 mg. of ascorbic acid daily. Five women developed postoperative uretero-vaginal fistulas, 2 of which healed spontaneously; 2 developed vesico-vaginal and 4 recto-vaginal fistulas. It is hoped to decrease this incidence by decreasing the radium dosage and increasing deep therapy. Of the 95 patients 29 have survived 5 years or more. Residual and apparently viable cancer was found in the surgical specimens of 26 of the 95 women (28 per cent). In 18 there was residual cancer in the cervix; in 2 other cases cells were found in the lymphatics of the uterus, in 5 in the pelvic lymph nodes and in one in the right ovary. The author believes that the 26 women with residual cancer benefited by the radical operation though 5 of them ultimately died of recurrent cancer. Some may contend that in those women who had no residual cancer the operation was done needlessly. As, however, 3 of these ultimately died of recurrent cancer not only was the operation necessary but it probably should have been more radical and thorough. Since we cannot tell which patients need the operation, and since it is usually too late by the time recurrence is clinically detectable, the reason for doing the operation after irradiation seems valid. His data demonstrate that deep irradiation undoubtedly kills off a good deal of the carcinoma that is metastatic in the pelvic lymph nodes.

[One is left with the impression that the author has not quite made up his mind about the place of combined therapy in cancer of the cervix, especially as he reminds the reader that it is still in the experimental stage, and that "the indicated treatment of cervical carcinoma today is irradiation of the cervix and pelvis".

This is a valuable account of personal experience with a frank statement of difficulties and disappointments by a distinguished operator. It should be studied in the original by all who still perform the "radical" operation for cancer of the cervix.]

F. J. Browne

213. **Does More Radical Surgery for Carcinoma of the Cervix Improve the Results?** (Lassen sich die Heilungs-Ergebnisse der Schauta- und der Wertheim-Operation beim Kollum-Karzinom durch weitere Radikalisierung verbessern?)

By K. J. ANSELMINO. *Geburtsh. u. Frauenheilk.*, **21**, 120–127, Feb. 1961. 2 tables. 3 figs. 5 refs.

In 2½ years the author performed the Schauta-Stoeckel operation on 111 patients with carcinoma of the cervix; all the patients had stage I or II tumours, except for 4 with stage III growths. The five-year cure rate was 76 per cent. In the succeeding 3½ years the same surgeon operated on 184 women with carcinoma of the cervix (5 were stage III), but during this time the more radical technique of the Schauta-Amreich operation was used; the five-year cure rate was 71 per cent. By comparing his own results with those of Meigs and the controlled series from Antoine's Clinic in Vienna (see abstract No. 400, *J. Obstet. Gynaec. Brit. Emp.*, 1959, **66**, 1056), Professor Anselmino concludes than an increase in the extent of operations for carcinoma of the cervix is not necessarily associated with an improvement in the results.

Peter J. Huntingford

214. **The Value of Post-Operative Irradiation in Cases of Carcinoma of the Cervix.** (Zur Bedeutung der post-operativen Nachbestrahlung beim Kollumkarzinom.)

By W. HELBING. *Zbl. Gynäk.*, **83**, 513–518, Apr. 1, 1961. 3 tables. 9 refs.

The unsolved problem of whether to administer radiotherapy after radical surgery is studied by the author in a review of a series of 504 cases of stage I carcinoma of the cervix. Of 262 cases treated by surgery alone, 74 per cent remained free from recurrence after 5 years. Of 242 patients treated by surgery followed by X-ray therapy, 76 per cent remained free from recurrence after 5 years. Of the patients treated with surgery alone 50 (19 per cent) developed a recurrence which was treated by irradiation, and of these 6 remained free from further recurrence. Of 242 patients treated with surgery and post-operative irradiation, 30 (12 per cent) required further radiotherapy for recurrence and 3 of these have again remained free from recurrence after 5 years.

It appears that post-operative irradiation did not produce any significant improvements in the results. If any viable cancer cells remain after radical surgery, it is not easy to understand why supplementary irradiation fails to improve the results. The author suggests that there are three possible explanations: (1) the radiotherapeutic technique may be inadequate and the dosage insufficient particularly as regards lymph nodes on the lateral pelvic walls. (2) Possibly as a result of the surgical treatment reduced oxygen supply in the operation area may diminish the effectiveness of irradiation. (3) Processes of inflammation and repair in the operation field reduce the response of cancer cells to radiotherapy. *Bruce Eton*

215. **Remote Results of the Treatment of Malignant Neoplasms of the Ovary with Surgery and Complementary Radiotherapy (X-rays and Cobalt Therapy).** (Risulati a distanza dell'exeresi chirurgica e della terapia attinica complementare (roentgen e telecobalto) nelle neoplasie maligne dell'ovaio.)

By M. CARBONINI. *Ann. Ostet Ginec.*, **83**, 107, Feb. 1961. 17 refs.

This is a detailed study and follow-up of 113 women operated on for malignant disease of the ovary between 1954 and 1960 at the Clinic of Obstetrics and Gynaecology at Milan.

The following conclusions are given:

The remote prognosis depends on the stage of invasiveness of the tumour at the time of operation. In 4th stage cases, which make up about 50 per cent of the present series, the disease is fatal in a short time in 85 per cent of cases. X-ray or cobalt therapy did not materially alter the prognosis. Pre-operative treatment with cobalt therapy and anti-malignant drugs such as antiblastic, cystostatic and antigonadotrophic drugs may make operation possible in apparently hopeless cases. In stage 3 cases where complete operative removal is not always possible complementary X-ray therapy may lower the mortality to 30 per cent.

In early cases, stage 1 and 2, the results are so good with no deaths in 35 cases that it is felt that a more conservative approach may be advocated, especially in younger women and in those in whom the disease complicates pregnancy. *Josephine Barnes*

216. **Management of Endometriosis with Nor-progesterone.**

By T. B. LEBHERZ and C. D. FORBES. *Amer. J. Obstet. Gynec.*, **81**, 102–110, Jan. 1961. 7 tables. 9 figs. 4 refs.

This is a report of the results of treatment of 112 cases of endometriosis. Two progestins were used, Norbutin (Parke Davis & Co.) and Enavid (Searle & Co.). The doses of both consisted of 10 mg. daily for 2 weeks, then 20 mg. daily for 2 weeks, then 30 mg. daily for 8 months. If break-through bleeding occurred the dose was increased 10 mg. daily until bleeding was controlled. At no time did daily dosage exceed 60 mg. This therapy caused pre-menstrual-like changes in the endometrial stroma cells and in the glands, followed by cellular degeneration, but so far no definitive conclusions regarding the final morphological changes in the ectopic tissues could be formulated, though in 1 case a recto-vaginal septum endometrioma seemed to have disappeared after 9 months treatment.

Of the 112 patients "it is felt that 85 (77·6 per cent) can be considered as clinically and symptomatically cured". They state that "they feel better after treatment than they have done for many years. Their comments as to correction of dyspareunia were especially gratifying." Five cases were considered failures from all standpoints—grossly, microscopically and symptomatically, though all showed good decidual effect on the endometrium. Side effects were nausea and vomiting which disappeared spontaneously after 4 to 6 months therapy, emotional distress, depression, and in 4 cases fibroids grew rapidly.

The authors conclude that nor-progesterone does affect ectopic endometrium favourably, and can be expected to give subjective and objective relief in 75 to 80 per cent of cases. They feel that it should be restricted to patients of 35 years and under, especially when child bearing is to be considered. *F. J. Browne*

OPERATIONS

217. **The Presence of Pathogenic Organisms in Modern Anaesthetic Equipment.** (Das Vorkommen von pathogenen Keimen in modernen Narkosegeräten.)

By W. MOSLER. *Zbl. Gynäk.*, **83**, 432–437, Mar. 18, 1961. 1 fig. 2 tables. 15 refs.

There is an undoubted risk of anaesthetic apparatus becoming infected during use, and as a result subsequent patients may become infected. The author carried out bacteriological examination of the individual components of routine anaesthetic equipment. He found that contamination was maximal in the parts nearest to the patient. It was more marked in the rubber tubing and rubber bag than in the connecting pieces made of metal. The soda lime remained free from infection. The commonest organism found was haemolytic *Staphylococcus aureus*.

After use the various parts were scrubbed and cleaned inside and outside with hot water and then "sterilized" with pressurized steam at 134° C., metal for 10 and rubber parts for 5 minutes. Subsequent bacteriological investigation showed, however, that this method failed to sterilize anaesthetic equipment made of rubber. Steam sterilization was therefore replaced by immersion of rubber parts in 70 per cent ethyl-alcohol for 60 minutes. In order to prevent subsequent contamination before actual use, all sterilized equipment was wrapped in sterile towels.

[This important problem does not seem to have received sufficient attention in the world literature.]

Bruce Eton

218. **Secondary Haemorrhage due to Bacteria causing Fibrinolysis after Vaginal Operations.** (Blutungen nach vaginalen Operationen durch fibrinolysierende Bakterien.)

By O. PREISLER. *Zbl. Gynäk.*, **83**, 456–459, Mar. 25, 1961. 2 tables. 23 refs.

The author cultured vaginal swabs obtained from 39 patients one day before and eight days after vaginal operations. He found that in about half the patients fibrinolytic bacteria were present before the operation, and in 17 afterwards, but the patients with positive pre- and post-operative findings were not identical. The bacteria detected which were capable of producing fibrinolysis were *Escherichia coli*, *Bacterium vulgare*, *Micrococcus pyogenes*, corynebacteria, enterococci, and beta-haemolytic streptococci.

In other patients methods of inhibiting the growth of these organisms were tried out, and in a second series of 36 patients it was found that daily instillation of a solution containing 100–125 mg. of tetracycline from the 4th to the 7th post-operative day proved to be effective. This treatment is suggested for the prevention of secondary post-operative haemorrhage. In order to reduce the development of drug-resistant organisms, the author recommends that treatment should only be given if bacteriological investigation on the third post-operative day demonstrated the presence of fibrinolytic bacteria.

Bruce Eton

219. **Hypogastric Sympathectomy: A Follow-up Assessment.** (I resultati a distanza della resezione del simpatico lombo-sacrale nelle plexalgie ipogastriche.)

By C. GIORNELLI. *Minerva ginec., Torino*, **12**, 1182–1187, Dec. 15, 1960. 6 tables. 100 refs.

The results of a follow-up of 100 operations after at least a year and at most over 7 years is recorded. Dysmenorrhoea was completely relieved in 85 per cent and benefited in 5 per cent, and there were good results in dyspareunia with resultant increase in libido. No disadvantages have been encountered. It is noted that labour pains can be almost completely absent after this operation, in fact one woman was admitted with full dilatation and a ruptured uterus, having had no symptom of pain.

W. C. Spackman

220. **Tubal Insufflation: Interpretation of Chymographs.** (La nostra esperienza in tema di insufflazione utero-tubarica chimographica.)

By P. MENTASTI. *Minerva ginec., Torino*, **13**, 68–84, Jan. 31, 1961. 39 figs. 58 refs.

Although the usefulness of testing the patency of the Fallopian tubes by the passage of carbon dioxide through them is contested by some authorities, it is a procedure very widely practised. Information supplied by a chymographic reading can reveal not only whether the tubes are patent but whether there is some organic or functional defect which renders the woman relatively infertile. Some of these conditions are amenable to corrective treatment.

The Fallopian tubes show considerable variation in contractility and sensitivity. It is believed that they can be influenced by the following factors—the psychological make-up of the individual, the timing of the insufflation with respect to the menstrual period, and the technique of the insufflation itself. The tubes are held to show a variable but appreciable spasticity at the time of ovulation and in apprehensive individuals, and occasionally to unnecessary stimuli associated with the type of cannula used. The normal chymogram will, after perhaps a short initial spasm, show a tracing around the 100 mm. Hg mark with regular small waves every 10–15 seconds. The initial spasm can in such cases be readily overcome by intravenous injection of an antispasmodic such as papaverine or hydergine. In a spastic tube the initial rise is higher and more prolonged and the reading throughout tends to be higher and with more pronounced waves. In stenotic tubes the reading is positive but at a high level (circa 200 mm.) and with peristaltic waves absent or ill-defined. In menopausal women the waves are small, flattened or absent.

As regards the characteristics of the chymogram at various dates in the menstrual cycle, no constant findings are recorded though in general the waves are larger and more frequent in the follicular phase than subsequent to ovulation. Insufflation should be carried out prior to ovulation and a plastic cannula of flexible type should be used which obtains its purchase on the cervix by a suction cup. The gas used is of course carbon dioxide and it is passed at the uniform rate of 40 c.cm. per minute.

W. C. Spackman

221. **Transitory and Permanent Functional Disturbances of the Bladder in Women Subjected to Radical Hysterectomy.** (Les troubles fonctionnels vésicaux transitoires et permanents chez les femmes operées d'hystérectomie radicale).

By E. ROBECCHI and C. MORRA. *Gynéc. prat.*, **12**, 7–22, 1961. 9 figs. 88 refs.

Functional lesions of the bladder are the commonest urinary complications of radical hysterectomy for carcinoma of the cervix. As such complications are rare after total hysterectomy, it must be that the anatomico-physiological cause of these bladder disturbances lies in the amount of tissue removed from the parametrium and pelvic walls.

The authors have studied the functional bladder anomalies in 37 women treated for stage 1 or 2 carcinoma of the cervix by radical hysterectomy and pelvic lymphadenectomy. These patients have been followed from the 15th post-operative day for 2 to 3 years. The method of study used has been the cystomanometer of Lewis.

The first assessment of each patient has been made about 15 days after operation and has shown, consistently:

1. A diminution in tone of the empty bladder.
2. The persistence of a low tone throughout the early stages of bladder filling.
3. After a certain degree is reached there is a steady rise of 4 to 10 mm. of mercury in bladder tone with the introduction of each 50 ml. of fluid into the bladder.
4. In about 50 per cent of these patients the bladder capacity is lower than normal but in the rest it remains normal.

At the same time as these cystomanometric readings have been made the authors have noted the following clinical points.

1. In 8 of their 37 patients, slight difficulty of micturition has occurred when this function was normal pre-operatively.
2. In 9 patients, overflow incontinence was present.
3. "Two stage micturition", i.e., micturition initiated only by manual compression of the lower abdomen or by coughing in 10 cases.
4. Total retention of urine in 10 patients.
5. In all cases a residual urine of 100 to 400 ml. was found.

These abnormalities tended to improve over a period of 4 to 12 months, but when the 34 surviving patients were reassessed 2 or 3 years post-operatively, 18 of them still had urinary symptoms. These were:

1. A loss of normal perception of the need to micturate (7 patients).
2. Inability to initiate micturition without mechanical assistance, such as abdominal compression (4 patients).
3. Two- or three-stage micturition (2 patients).
4. Stress incontinence (3 patients).
5. Residual urine of 100 to 300 ml. (6 patients).
6. Complete urinary retention (2 patients).

Frequently more than one lesion was present in the same patient and it was therefore difficult to obtain cystomanometric records characteristic of each lesion.

However the two patients with complete retention showed records indistinguishable from those recorded in the immediate post-operative period.

In their discussion the authors raised two main points:

1. Why do these urinary difficulties follow radical hysterectomy and not the simple operation?
2. Why do 50 per cent of patients recover normal bladder function?

They feel that the answer to the first question lies not so much in the bladder ischaemia produced by the operation, and to which a great deal of attention has been drawn, as in the interruption of the nerve supply of the bladder that occurs in such radical procedures. They suggest that the recovery of bladder function is due either to a regeneration of the nerve tracts or the development of local control by the bladder. The persistence of bladder dysfunction is explained by incomplete regeneration of the nerves or imperfect adaptation of the local control.

They do not feel that the frequency of these disturbances should deter the gynaecologist from the practice of radical hysterectomy as a method of treatment of carcinoma of the cervix. *Geoffrey Dixon*

222. **Prevention of Fistulas and Lymphocysts in Radical Hysterectomy.**

By R. E. SYMMONDS and J. H. PRATT. *Obstet. and Gynec.*, **17**, 57–64, Jan. 1961. 4 figs. 8 refs.

By complete peritonealization of the pelvic floor in the operation of radical hysterectomy (extended Wertheim) and draining of the pelvis by means of extra-peritoneal suction catheters the authors claim that the incidence of post-operative fistula and lymphocyst formation is reduced. Out of the 38 cases reported, 20 had the suction catheters inserted. These were put through stab wounds in the inguinal area down to the obturator fossa extraperitoneally. The peritoneum is closed by approximating the peritoneum of the bladder to the anterior wall of the vagina, and the peritoneum of the rectosigmoid to the posterior aspect of the vaginal cuff. When this has been done, a second layer of sutures approximates the bladder and recto-sigmoid peritoneum, thus completely closing the peritoneal cavity. *J. G. Dumoulin*

223. **Autopsy Comparison of Cardiovascular Changes in Castrated and Normal Women.**

By E. R. NOVAK and T. J. WILLIAMS, *Amer. J. Obstet. Gynec.*, **80**, 863–869, Nov. 1960. 5 tables. 22 refs.

It has been claimed as an argument against removal of both ovaries when hysterectomy is done in premenopausal women for some non-malignant condition that it is likely to cause cardiovascular changes and coronary artery disease. The authors have carried out a post-mortem study of the incidence of these diseases in 61 women who had both ovaries removed at least 10 years before death, and compared it with the incidence in 256 controls. Fourteen of the 61 women had had their ovaries removed before 30 years of age and 25 between 30 and 40 years. No significant difference was found in the incidence of arteriosclerosis between the castrated women and the controls regardless of the age at operation or the number of years before death. *F. J. Browne*

224. **The Use of the Foley Catheter in the Surgical Treatment of Vesico-Vaginal Fistulae.** (Utilisation de la sonde de Foley dans la cure chirurgicale des fistules vésico-vaginales.)

By P. BARROS. *Gynéc. prat.*, **11**, 383–390, 1960. 14 figs.

The author describes his extremely simple method of making use of a Foley catheter to render a vesico-vaginal

fistula more accessible to surgery and to facilitate the necessary dissection. The collapsed catheter is introduced into the bladder through the fistula. The balloon is then inflated and by making traction on the catheter the fistula is brought within easy reach.

A transverse incision is made above the cervix on the anterior vaginal wall and an ellipse of skin around the fistula excised. If the repair is being undertaken within fifty days of the first appearance of the fistula it is enough to close the opening into the bladder by a purse-string suture of catgut which is inserted whilst the Foley catheter is still *in situ* but is not tied until the latter has been removed. This original purse-string is reinforced with a second and then a final layer of interrupted Lembert sutures. The vaginal incision is then closed in the form of an inverted T by interrupted catgut sutures. The author advocates early closure along these lines most emphatically, but if for some reason closure is delayed more than fifty days he thinks that the only modification required is more extensive mobilization of the bladder and the excision of the edges of the fistula.

Post-operatively a normally inserted Foley catheter is used for continuous drainage but the author instils one mega unit of soluble penicillin made up in 5 ml. of normal saline into the bladder some 3 to 5 times a day.

Patients who have had a vesico-vaginal fistula repaired in this way may safely be delivered vaginally in subsequent pregnancies unless the cause of the fistula is likely to be recurrent. If the vesico-vaginal fistula has involved the sphincteric portion of the bladder neck and urethra, however, and the repair has resulted in good urinary control he feels a Caesarean section is the wisest course.

[Whilst the reviewer has no personal experience of this method the simple use of a Foley catheter does seem an admirable way of rendering the "hard to get at" fistula more accessible.]

Geoffrey Dixon

225. **The Inguino-vaginal-retropubic Sling Operation in the Treatment of Relative Urinary Incontinence in Women.** (Operazione dell'ansa inguino-vaginale-retropubica per il trattamento della incontinenza urinaria relativa nella donna.)

By V. Fiaccavento, G. Narik and H.-H. Palmrich. *Ann. Ostet. Ginec.*, **82**, 1179, Nov. 1960.

The three authors describe an operation devised and practised in the University Clinic in Vienna. It is used in cases of urinary incontinence in women. It is not suitable for cases where there is a neurological cause, cystitis, malignant disease or vesico-vaginal fistula.

A fascial sling is cut in the inguinal region on each side, parallel to the inguinal ligament. This is passed into the retropubic space. The two slings are then brought down through a vaginal incision and sutured beneath the urethra.

The operation has the advantage of easy performance and gives good results in severe cases and in relapses. It may also find a place in simple cases of stress incontinence.

Josephine Barnes

UROLOGY

226. **The Significance of Urological Changes prior to Treatment for Cancer.** (Die Bedeutung urologischer Veränderungen vor der Krebsbehandlung.)

By H. Pockrandt. *Zbl. Gynäk.*, **83**, 437–443, Mar. 18, 1961. 2 figs. 1 table. 27 refs.

In many patients suffering from gynaecological cancer after radical surgery, urinary abnormalities are discovered which may have been present partially or wholly before operation. One hundred and forty patients were subjected to systematic urological investigation including renal clearance tests before radical vaginal surgery. Inflammatory processes were found in 4·3 per cent, "reactionary" changes in the bladder in 17 per cent, various degrees of ureteric obstruction in 4·9 per cent, and malformations in the urinary tract in 1·4 per cent. Eighteen patients gave a history of previous urinary disease, but did not show any abnormal findings on cystoscopy, yet 7 of these had post-operative cystitis or renal complications.

The incidence of pre-operative urinary abnormalities related to the different stages of cervical cancer was as follows: stage 0, 5 per cent; stage 1, 5·45 per cent; stage 2, 37·5 per cent; stage 3, 73·3 per cent. As the prognosis is so much worse in cases with pre-operative ureteric obstruction, the author wonders whether this fact should not be considered in the clinical staging of cervical cancer.

The frequency of positive pre-operative urological abnormalities indicates that full investigation of the urinary tract should be carried out as a routine before considering radical surgery in these cases.

Bruce Eton

227. **Urinary Incontinence in Women.**

Gynéc. prat., **11**, No. 6, 437–597, 1960.

The whole of this issue is devoted to urinary incontinence in the female. It contains 15 original articles which embrace a wide field of the pathogenesis, diagnosis and treatment of the condition.

Much of the material presented can be found by reference to any standard gynaecological textbook printed in the English language, and in reviewing it one has to bear in mind the words of the Editor in the preface to this issue of the journal. "Urinary incontinence has interested French gynaecologists little or not at all. In his desire not to cross the frontiers of one speciality, the French gynaecologist has restricted himself to the female genital system and its related endocrine glands. Until very recently, when a patient had both incontinence and a prolapse, the gynaecologist confined himself to treating the latter and left the urologist to cure the incontinence."

It is obvious that French gynaecologists, at any rate those interested in the production of this journal, have decided that this unsatisfactory state of affairs must now end and that they must be prepared to deal with the more common problems of female urology as are their British and American colleagues.

It is not feasible to review all the articles individually and would be invidious to select some to the exclusion of others. The overall impression is that the subject of urinary incontinence has been taken up with true Gallic enthusiasm but that this enthusiasm has not excluded the equally French characteristic of individuality.

Many of the widely accepted British and American ideas on the subject incur severe and often well-founded criticism, and new concepts in aetiology and diagnosis are put forward, including a description of forms of urinary incontinence due to hormone imbalance.

Whilst it seems unlikely that any number of the articles contained in it will become classic references on the subject of "sphincteric incontinence" (a term which is here preferred to stress or orthostatic incontinence) perusal of this journal is both interesting and stimulating.

Geoffrey Dixon

228. **Urovaginal Fistula: A New Device for Effective Control of Urinary Incontinence.**

By A. H. MILBERT. *Obstet. and Gynec.*, **16**, 743–744, Dec. 1960. 1 ref.

The author has modified the vaginal rubber cup (devised by Liswood for the collection of menstrual fluid) in order to control urinary incontinence due to a fistula from the urinary tract into the vagina.

To the conical cup which occludes the vaginal orifice he has attached a rubber tube and urinal bag. The bag is attached to the upper thigh. The apparatus is inserted and removed by the patient herself, and works satisfactorily.

J. G. Dumoulin

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